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Edited by David B. Paintin

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January 1989, Vol. 96, pp. 1–3

COMMENTARY

Maternal mortality in developing countries

Until comparatively recently in international health circles, the significance of pregnancy-related deaths was accorded a very low priority. Fortunately, a sense of realism has now prevailed as reliable information begins to spread.

Current estimates of maternal deaths per 1000 births are 6·4 in Africa, 4·2 in Asia, 2·7 in Latin America, 0·3 in all developed countries and less than 0·1 in Middle and Northern Europe (Editorial 1987). Of the estimated half a million maternal deaths worldwide each year, 150 000 take place in Africa, 282 000 in Southern and South Eastern Asia, 26 000 in Western and East Asia, 34 000 in tropical South America, 1000 in temperate South America, about 2000 in Oceania, giving a total of 494 000 maternal deaths in developing countries and 6000 in all developed countries (unpublished World Health Organization sources). There are more maternal deaths in India in 1 day than there are in all developed countries in 1 month. Even more depressing is the realization that in parts of West Africa (Greenwood *et al.* 1987) current maternal death rates at over 20 per 1000 births are the same as those in England in the 16–18th centuries (Dobbie 1982). Morbidities such as obstetric fistula from obstructed labour, banished ages ago in industrialized countries, are still with us in Africa: 1000 women with obstetric fistula await treatment in one hospital in an African city.

Such international and historical comparisons indicate that in places where maternal death rates are still high, this is due to the existence of serious defects in the social, economic and political conditions and to the fact that health care services are grossly inadequate in quantity and quality. In such environments, the common causes of maternal deaths—abortion, anaemia, eclampsia, infection, haemorrhage, obstructed labour and its complications—are related to the neglect women suffer, the low esteem in which they are held in their societies, and the ignorance of the general population. On the economic front, the current debt crises impose further strain on the already fragile economies; poverty and starvation are increasing and social inequity is deepening.

Clearly, if the high maternal mortality rates are to fall, action is needed not only in terms of health intervention policies but also on other fronts. The approach has to be global in scope, and so the developed countries have a major role to play. They possess the necessary finance and technology, lacking in developing countries. Equally certain is the fact that the mere provision of finance and technology is not enough. Major political changes aimed at modernization of the social and political structures are needed so as to ensure that the aid from the developed countries is used effectively. But then, without universal formal education, it is difficult to see how modernization can be achieved. Universal formal education is the most effective weapon against social inequity, and it has a very favourable influence on reproductive behaviour When compared to illiterates, educated women bear fewer children and achieve better child survival. Early teenage marriage, pregnancy under the age of 16 years and over the age of 35 years, high parity and lack of antenatal care are all well-documented high-risk factors which educated women avoid much more than their illiterate sisters (Harrison *et al.* 1985); they also avoid harmful cultural practices.

Much as we may want to modernize our societies in order to improve maternal health, obstacles abound. Some cherished traditional customs are sure to be discarded as modernization begins to take effect. Those within the society whom these traditional customs favour would not willingly welcome the change. Outsiders are often curious about many traditional customs and would want to see them preserved for as long as possible (female circumcision excepted) believing that whatever is old is well tested and better.

Reducing the high maternal mortality rate in

Third World countries is a challenge which political leaders will do well to accept and there are signs that they are willing to do so; they will look to the health professionals and policy makers for guidance. If the truth has to be told, the fact is that the existing health services in most Third World countries are grossly underfunded and serious flaws exist in the way they operate, so that people have no confidence in them. Scant attention is paid to the key elements on which maternal survival depends. These are that general living standards must be good, so that an increasing proportion of the population is healthy; all pregnant women must receive basic but professional antenatal care; measures must be taken to ensure that when complications requiring operative intervention develop, prompt treatment is given (Editorial 1987). The treatment and prevention of all the major obstetric causes of death are common knowledge, as are the organizational structures which support the basic principles enunciated above. Thus, restructuring the existing health services to allow the principles stated above to apply is important, and information on how to do it is available (WHO 1988). However, health service restructuring must not be seen in isolation. Its success is heavily dependent on developments in other fields. If an unbooked woman dies of obstetric haemorrhage after travelling 200 km from her village to a hospital, failures in a chain of events are collectively responsible for her death, not just the haemorrhage. A major problem in this case could be poor transportation and communication. One solution is the building of a maternity waiting home at the hospital site. In it, women from remote villages with high-risk factors can live during the last weeks of their pregnancies, so that whenever labour starts, delivery can be conducted with safety in the hospital. Cuba is among the countries which have taken this step with resounding success. Each locality can work out for itself, guided by the application of health systems research, strategies that can make similar impact in reducing obstetric deaths.

Outsiders have made enormous contributions to better maternal health in developing countries. But sometimes without knowing it, the plans they advocate are detrimental to women's interest, in that the actions reinforce rather than weaken harmful traditional customs. Where women are dying in their thousands from haemorrhage, anaemia and obstructed labour, we are being told to fall back on traditional medicine as if traditional medicine has the answer to the arrest of haemorrhage from a ruptured uterus. Family planning is an important service for international donor agencies to promote. However, if the full impact of fertility control in saving maternal lives and in checking population growth is to be felt, then family planning promotion must go hand in hand with proper growth in the economic, educational and health sectors (Mahler 1984); sadly this is not yet the case (Round the World 1988). Another disturbing idea being promoted concerns caesarean sections. Desperate for instant success, some policy-makers argue that in places where physicians are scarce, non-physicians should be trained to perform caesarean sections (White *et al.* 1987). We would have hoped that thorough consideration would have been given to the long-term consequences of this policy, but it appears that this is not so.

Perhaps the most contentious of all is the retraining of illiterate traditional birth attendants (TBA). The inherent disadvantages of this strategy and its failure in reducing maternal mortality in Africa and Asia are discussed in detail elsewhere (Harrison 1980; Editorial 1983). Another criticism of this strategy is that it does not fit in with the concept of modernization. Experience in both the developed countries and in the newly industrialized developing countries teaches that as formal education spreads and mass illiteracy disappears, reliance on the TBA falls and eventually ceases altogether. If, therefore, we want to reduce maternal mortality through modernization, which we should, the idea of strengthening the activities of the TBA while at the same time encouraging the spread of formal education is like sprinting on mud. It is futile. Well-meaning organizations are of the opinion that the promotion of retraining programmes for the TBA is a temporary measure implying that it will soon be discarded for something better suited to women's real needs. But these programmes for retraining have been in operation since 1921, beginning in the Sudan. During these 67 years, the combined effects of modernization and prosperity have sharply reduced maternal deaths elsewhere, whereas under the harsh living conditions in Africa and most of Asia where the TBA chiefly operates, her activities have not improved the dreadful maternal outcomes. The TBA is very much part of the outdated and dangerous system of maternal health care. If her deployment continues after 'retraining', this will be tantamount to replacing one bad system with another. The tragedy will then be that action taken later to institute a well-organized modern system of care becomes harder to effect. Doubtless, retraining the illiterate TBA is challenging, but real progress in reducing maternal mortality will come by directing attention not on the TBA but on the training and proper utilization of midwives.

If examples are needed to prove the points made in this commentary about preventing the carnage in the Third World, the two articles published in this issue provide them. Hong Kong has accepted modernization, its gross domestic product has risen 14-fold in two decades, and although its population has risen by nearly 70% during roughly the same period, its maternal mortality rate is now in line with the lowest in Europe (Duthie *et al.* 1989). By contrast, the Menoufia Governorate of Egypt has not yet accepted modernization fully, judging from the high illiteracy rates. So there is failure to organize, to accept and to use what is known to be good, resulting in the high maternal mortality rate reported in this Journal (p.9) by El Kady *et al.*

But all is not lost. The enthusiastic support for reducing maternal mortality is growing worldwide, beginning with the pioneering efforts of the Royal College of Obstetricians and Gynaecologists (Philpott 1979), so that the best is yet to come. We hope it comes soon and in the right direction where the eradication of mass illiteracy through universal basic formal education is given the highest priority. If we fail to eradicate mass illiteracy, all the indications are that even the small initial gains we may make in reducing maternal mortality will slip away from us, and in the end, hardly anything will be left to show for our efforts.

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Maternal mortality in Hong Kong 1961–1985

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Summary. The maternal mortality rate in Hong Kong fell from 0·45/1000 total births in 1961 to 0·05/1000 total births in 1985. During the period between 1961 and 1985 there were a total of 438 maternal deaths and 2 193 012 births. Of the 438 deaths 150 (34%) were due to haemorrhage during pregnancy and childbirth (ICD 640, 641, 666), 89 (20%) were due to pre-eclampsia (ICD 642, 643) and 60 (13·7%) were due to ectopic pregnancy (ICD 633). Comparison of maternal deaths by cause between the periods 1961–1965 and 1981–1985 showed an 86% reduction in deaths due to haemorrhage and pre-eclampsia and a 72% reduction in deaths due to ectopic pregnancy. Pulmonary embolism was not a major cause of maternal mortality.

It is recognized that the maternal mortality rate is both a means of judging the standard of obstetric care provided and a sensitive index of health and socio-economic well-being in the society (Hogberg 1985). We examined the causes of maternal mortality in Hong Kong between 1961 and 1985 and have also speculated on the possible reasons for the striking fall in the maternal mortality rate.

Subjects and methods

The study period was between 1961 and 1985. A 'year' corresponds to the financial year in Hong Kong which is from 1 April to 31 March of the following year. During the study period there were 438 maternal deaths and 2 193 012 total births. A maternal death is defined as death during pregnancy or within 42 days of an abortion or delivery. The International Classification of Diseases, Injuries and Causes of Death (ICD ninth revision) was taken as the source of definitions for the classification of maternal deaths. The annual departmental reports of the Director of Medical and Health Services, Hong Kong, for the years 1961 to 1985 were the sources of data concerning maternal deaths. The information contained in the reports is based on the entries which were made in the patients' death certificates. The reports were also used as the source of data for perinatal mortality rates, numbers of total births in Hong Kong, birth rates, population size, and numbers of hospital beds per 1000 population. All births in Hong Kong are registered. Enquiry was made at the Department of Medical and Health Services to obtain information on the number of legal abortions carried out in Hong Kong. The Director of Medical and Health Services must be notified of all legal abortions carried out in Hong Kong under 47A of *The Offences Against The Person Ordinance.* Information on the changes in numbers of total births, birth rates and numbers of legal abortions was used to establish trends in parity in Hong Kong.

Results

The maternal mortality rate in Hong Kong (expressed per 1000 total births) fell from 0·45 in 1961 to 0·05 in 1985. The highest maternal mortality rate during the study period was 0·48 and

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occurred in 1962, the lowest rate was 0·01 during 1982 (Fig. 1). The perinatal mortality rate in Hong Kong dropped steadily from 26·3/1000 total births in 1961 to 7·7/1000 total births in 1985. The birth rate dropped steadily from 35·0/1000 population in 1961 to 14·1/1000 population in 1985. The population of Hong Kong grew from 3 168 100 in 1961 to 5 422 800 in 1985.

The main causes of maternal mortality were haemorrhage during pregnancy and childbirth (ICD 640, 641, 666), ectopic pregnancy (ICD 633) and pre-eclampsia (ICD 642, 643). Of the 438 maternal deaths during the study period 150 (34%) were due to haemorrhage, 89 (20%) were due to pre-eclampsia and 60 (14%) were due to ectopic pregnancy. These three causes accounted for 68% of all the maternal deaths in Hong Kong over the study period. Table 1 shows the distribution of maternal deaths by cause between two periods, 1961–1965 (inclusive) and 1981–1985 (inclusive). The numbers of deaths due to each of the three main causes and due to other causes have fallen considerably. Comparison of maternal mortality rate by cause shows an 86% reduction in deaths due to haemorrhage and pre-eclampsia and a 72% reduction in deaths due to ectopic pregnancy. However, the proportion of deaths due to haemorrhage and pre-eclampsia has not altered much whereas the proportion of deaths due to ectopic pregnancy has risen.

Pulmonary embolism was not a major cause of maternal mortality and was not categorized as such, whereas sepsis, which accounted for fewer deaths than any of the three major causes, was categorized separately. However, the exact number of deaths due to pulmonary embolism is unavailable. Sepsis (excluding septic abortions) was a comparatively minor cause of maternal mortality accounting for 16 (3·7%) deaths. The last maternal death due to sepsis during the study period was in 1979.

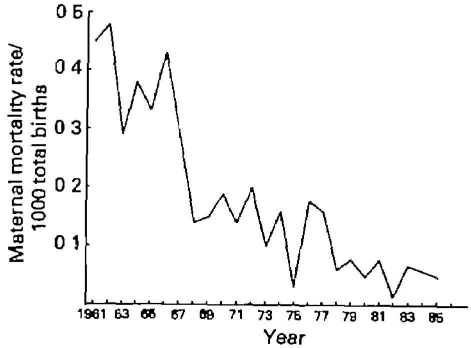

Fig. 1. Maternal mortality in Hong Kong 1961–1985.

The number of legal abortions carried out in Hong Kong increased from 184 in 1973 to 15 411 in 1985. Overall, between 1973 and 1985 there were 96 004 legally induced abortions. Between 1979 and 1985 there were no deaths due to legally induced abortion and one death due to illegally induced abortion. Figures for the period before 1979 are unavailable.

Discussion

In 1983, the maternal mortality rate in Hong Kong was 0·07 and was the lowest in Asia and among the lowest in the world. The figures for the maternal mortality rate per 1000 births in other countries in 1983 were 0·11 in Singapore, 0·15 in Japan, 0·38 in the Republic of Korea, 0·05 in the Netherlands and 0·05 in Switzerland (United Nations Organization 1986).

The striking fall in the maternal mortality rate in Hong Kong was achieved over a comparatively short time. It is not possible to identify retrospectively the factors present in individual cases of maternal death in Hong Kong as there is no system for confidential enquiry into maternal deaths. Thus, any attempt to explain the considerable drop in the maternal mortality rate would be speculative.

The total number of births per annum and the birth rate are dropping whereas the population size and the number of legal abortions are increasing. This indicates that parity has fallen. High parity is a risk factor for maternal mortality (Oxorn 1955; Rosenfield & Maine 1985) especially in areas where infant survival is also poor (Harrison *et al.* 1986). Obstetric complications which are associated with high parity include postpartum haemorrhage (Chassar Moir & Myerscough 1975), uterine rupture (O'Driscoll & Meagher 1980) and amniotic fluid embolism (Beazley 1981; Duff 1984). A study in Hong Kong showed that maternal mortality rates by parity were 41 per 100 000 total births if the parity was 0 and 82 per 100 000 total births if the parity was >5 (Yam *et al.* 1986). These observations support the speculation that the drop in parity contributed to the fall in the maternal mortality rate, but using the available data it is not possible to show that it was the high parity women who were the major group who died

Table 1. Maternal deaths in Hong Kong by cause, 1961–1965 and 1981–1985

	Maternal deaths			
	1961–1965		1981–1985	
Cause of death	*n* (%)	Rate/1000 births	*n* (%)	Rate/1000 births
Total births	546 672		409 508	
Total maternal deaths	214 (100%)	0·39	23 (100%)	0·056
Haemorrhage	77 (36%)	0·14	8 (35%)	0·019
Pre-eclampsia	49 (23%)	0·09	5 (22%)	0·012
Ectopic pregnancy	20 (9%)	0·036	4 (17%)	0·01
Sepsis	9 (4%)	0·016	0	—
Other causes	59 (28%)	0·108	6 (26%)	0·014

from haemorrhage in 1961 and who were no longer present towards the end of the study period.

Advanced maternal age is a risk factor for maternal mortality (Chabaud *et al.* 1983; Hogberg 1985; Ojo & Savage 1978; Oxorn 1955). Maternal mortality rates in Hong Kong per 1000 total births for different age groups between 1962 and 1983 were: <20 years, 0·11; 20–29 years, 0·14; 30–39 years, 0·52; >40 years, 1·73. During the period between 1962 and 1970, women over 35 years of age delivered at the teaching hospital constituted 16·2% of the total number delivered, whereas during the period between 1971 and 1980 the proportion had dropped to 8·6% (Ghosh *et al.* 1985). Thus, decreases in maternal age and parity may well have had a favourable influence on the maternal mortality rate.

Among the factors which make Hong Kong unique are its small size, high population density and the latent rewards of a newly industrialized state. Adverse living conditions are associated with higher maternal mortality (Harrison & Rossiter 1985; Harrison *et al.* 1986; Rao 1979; Llewelyn Jones 1974). Reports from India indicate that difficulties with transport led to maternal deaths which might otherwise have been preventable (Bhasker Rao 1975). In Thailand, maternal mortality rates in rural areas are higher than those in urban areas (Phuapradit *et al.* 1985). By contrast, Hong Kong's population is concentrated and both transport and communications are well developed. The maternal mortality rate is considered to be a sensitive index of health and socio-economic well-being in the society (Hogberg 1985). It is interesting to note that the gross domestic product of Hong Kong increased 14-fold between 1966 and 1985 (Census and Statistics Department 1987) and the maternal mortality rate dropped ninefold between 1961 and 1985.

In Hong Kong, all obstetric patients are attended by a doctor or midwife and all deliveries occur in institutions. This is a fundamental difference between Hong Kong and many developing countries where it has even been suggested that the maternal mortality rate be expressed as a fraction of expected rather than total births (Thuriaux 1984).

It is recognized that antenatal care (Harrison & Rossiter 1985; Kaunitz *et al.* 1984; Mashini *et al.* 1984), the availability of blood for transfusions (Stallworthy 1939; Yam *et al.* 1986), the use of oxytocics for the third stage (Martin & Dumoulin 1953), facilities for the adequate management of hypertensive disorders (Walker 1986), and antibiotics (Walker 1986) help to reduce maternal mortality. Such facilities are readily available in Hong Kong. Between 1961 and 1985 the number of hospital beds per 1000 population increased by 50% despite the increase in the population. We speculate that the improvement contributed to the decrease in the maternal mortality rate.

Causes of maternal mortality which are comparatively rare in Hong Kong are pulmonary embolism, abortion and sepsis. Pulmonary embolism is a major cause of maternal deaths in Western countries (Aaro & Juergens 1974; Bissell 1977; DHSS 1982, 1986). Deaths from abortion constitute a major component of the maternal mortality rate in other parts of Asia (Bhasker Rao 1975; Phuapradit *et al.* 1985; Rochat *et al.* 1981). Sepsis is a major cause of maternal mortality in Nigeria (Hartfield 1980; Ojo & Savage 1978).

Although the number of maternal deaths is small, it is nevertheless important to establish a perspective on individual causes of maternal mortality (Chamberlain 1985) so that changes may be noticed and the appropriate action taken. In the UK, the increasing incidence of primary postpartum haemorrhage as a cause of maternal mortality in primigravidae has been reported (DHSS 1982, 1986; Gilbert *et al.* 1987).

Currently, the maternal mortality rate is low in Hong Kong. As well as retaining the measure of maternal mortality rate, more emphasis should be placed on the analysis of severe maternal morbidity. Recent advances in intensive care expertise and technology have helped to reduce the maternal mortality rate and also to reduce the margin between mortality and severe morbidity (Derom *et al.* 1987). Thus, analysis of severe maternal morbidity together with maternal mortality would provide a more accurate assessment of the effectiveness of the services provided. Having brought the maternal mortality rate to its admirably low level the continuous, careful and critical appraisal of maternal morbidity will be among the tasks faced by contemporary obstetricians in Hong Kong.

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Obstetric deaths in Menoufia Governorate, Egypt

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Summary. A survey of all registered deaths which occurred during 1981–1983 in women of reproductive age was carried out in Menoufia Governorate, Egypt. Surviving family members were interviewed by trained social workers, and information was collected on symptoms of the disease that led to death. The completed questionnaires were reviewed by a panel of local physicians and a cause of death was assigned by the panel. Maternal mortality was a leading cause of death, second only to heart disease. There were 190 maternal deaths per 100 000 livebirths and 45 maternal deaths per 100 000 married women aged between 15 and 49 years. Most of the maternal deaths (63%) were due to direct obstetric causes of which haemorrhage was the main cause. Another 27% of the maternal deaths were due to indirect obstetric causes of which rheumatic heart disease was the main cause.

In developing countries, high parity, pregnancy at the extremes of reproductive life and short intervals between pregnancies account in part for high maternal mortality. Other factors such as poverty, malnutrition, customs and beliefs, inability or unwillingness to seek antenatal care, and environmental conditions exacerbate the situation.

In developed countries, the dangers of pregnancy have been overcome by medical improvements as well as by advances in the health and education of women. Use of contraception has helped these countries reduce their maternal mortality and the number of pregnancies in women in high-risk groups (teenagers, older women, and women of high parity). Effective and acceptable means of fertility control could prevent a quarter of the pregnancy-related deaths (Rochat *et al.* 1981; Fortney 1987).

The purpose of the Reproductive Age Mortality Survey (RAMOS) was to study all causes of death in married women of reproductive age in Egypt. The site chosen for the research was the Menoufia Governorate where the death registration system is almost complete. Menoufia, one of 27 Egyptian governorates, lies in the Nile Delta, 45 km north of Cairo (Fig. 1). Its 1·9 million people earn their living primarily from agriculture, although there is some light industry in the largest town. Illiteracy is still high, especially among women.

Administratively, Menoufia is divided into eight counties, with more than 300 villages some of which are quite large (population >20 000).

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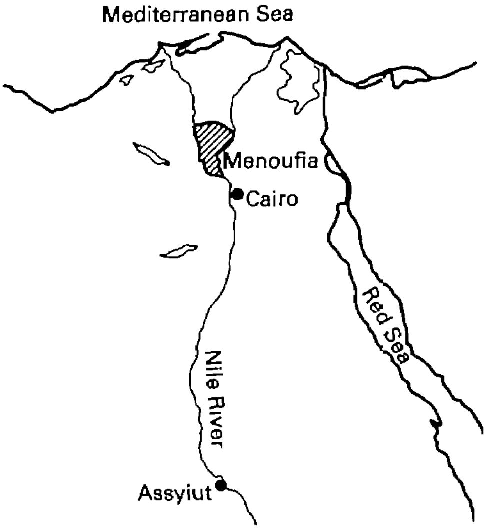

Fig. 1. Location of Menoufia, Egypt.

Health services consist of 11 general hospitals (1128 beds) and eight specialized hospitals (eye, chest, fever) in the county seats. There are also three smaller village hospitals. Basic health care is provided through 155 rural health units, each with one or two doctors (1345 beds), and 10 maternal and child health (MCH) centres which have specially trained doctors. Thus, the whole population is within easy reach of basic health care. There are also private clinics and several small nursing homes.

In Menoufia, as in the rest of Egypt, more than 90% of deliveries take place at home, most attended by a traditional birth attendant, the 'daya'. Fertility remains high (36 births/1000 population) and only 25% of fertile couples practice contraception.

During the 3-year study period, 1981–1983 inclusive, a total of 1691 deaths occurred in women of reproductive age (15–49 years) and 385 (23%) of these were due to maternal causes (Saleh 1987). The present paper examines the characteristics of these women, the causes of their deaths, and the proportion of maternal deaths due to pregnancy, delivery and indirect obstetric factors.

Subjects and methods

Deaths in women of reproductive age were identified from death registration lists. Trained social workers (non-medical interviewers) visited the families of the deceased and administered a standardized, pretested interview schedule on socio-demographic factors, reproductive and contraceptive history, and symptoms of the disease that led to death. The completed interview schedules were reviewed by a medical panel who assigned the cause of death. The panel consisted of a physician, a pathologist, an obstetrician/gynaecologist and specialists in infectious diseases and public health. The cause of death was coded using a modification of the WHO International Classification of Disease (ICD-9) Basic Tabulation List. The diagnoses were made by physicians who had had no contact with the deceased, although they did on occasion have access to clinical records. No autopsies were done during the 3-year period of the study. Autopsies are rare in Egypt and are only done when the police are involved in investigating the death, the district attorney asks for an autopsy in cases of suspected homicide or suicide, and for traffic accidents. Martin (1979) reported that post-mortem examination did not establish the exact cause of death in 23% of the cases, although the associated clinical features enabled a special medical committee to classify all but four cases. Even a full autopsy does not always allow a clear distinction between maternal cause and some other underlying cause (Puffer & Griffith 1967).

The following definition of maternal death was adopted from the Committee on Maternal Mortality of the International Federation of Obstetrics and Gynecology: 'Death of any woman dying of any cause while pregnant or within 42 days of termination of pregnancy, irrespective of the duration or the site of the pregnancy'.

Results

There were 190 maternal deaths per 100 000 live-births and 45 per 100 000 married women aged between 15 and 49 years. Maternal mortality was a leading cause of death accounting for 22·8% of all deaths that occurred in women of reproductive age, second only to diseases of the circulatory system which accounted for 28% of all deaths. There was a total of 385 maternal deaths of which 241 were due to direct obstetric causes and 21 were associated with abortion (Table 1). In 21 maternal deaths the exact cause was not known but was related to the pregnancy.

Table 1. Causes of 385 maternal deaths in Menoufia, Egypt, 1981–1983

	Maternal deaths	
Cause	*n* (%)	Per cent of all maternal deaths
Direct obstetric	241 (100)	62·6%
Haemorrhage	125 (51·9)	
Sepsis	44 (18·3)	
Toxaemia	38 (15·8)	
Associated with caesarean section	34 (14·1)	
Abortion	21 (100)	5·5%
Haemorrhage	11 (52·4)	
Sepsis	6 (28·6)	
Other	4 (19)	
Indirect obstetric	102 (100)	26·5%
Diseases of the circulatory system	65 (63·7)	
Infections and parasitic diseases	9 (8·8)	
Diseases of the respiratory system	5 (4·9)	
Diseases of the digestive system	5 (4·9)	
Diseases of the urogenital system	3 (2·9)	
Neoplasms	1 (0·9)	
Other	14 (13·7)	
Unknown	21	5·4

Characteristics of maternal deaths

Education. Of the 385 maternal deaths in Menoufia 296 (76·3%) occurred in illiterate women and only 26 (6·7%) in women who had a high-school education (Table 2).

Age and parity. Of the 385 maternal deaths 200 (52%) occurred in women who had given birth four or more times before, 181 (47%) in women of parity 1–3 and only 1% occurred in women having their first baby. Maternal mortality rises steeply with increasing maternal age (Augensen & Bergsjo 1984). The safest age for pregnancy is between 23 and 34 years of age (Buchanan 1975). In this study we found the risk of maternal death was 1·9 times greater in women ≥40 years of age than in women in their twenties.

Place and time of death. Most (53%) of deaths occurred at home, and most (59%) occurred during the postpartum period; 46 deaths (12%) occurred during pregnancy, and 112 deaths (29%) during labour (Table 2). These figures reflect the importance of postpartum care, taking into consideration the fact that events occurring in the antepartum and intrapartum periods may lead to death later in the postpartum period. Rapid death (<6 h after a complication) occurred in 24% of the maternal deaths, reminding us that a normal physiological event, childbirth, may quickly change into a dire emergency, particularly in the absence of appropriate antenatal and intrapartum care.

Direct obstetric causes

Of the 241 women who died of direct obstetric causes (Table 1), haemorrhage accounted for 125 deaths (52%), sepsis for 44 (18%), pre-eclampsia and eclampsia for 38 (16%) and caesarean section for 34 (14%).

Haemorrhage. Antepartum haemorrhage accounted for 52 deaths and postpartum haemorrhage accounted for 73 deaths. Patients with postpartum haemorrhage died more quickly

Table 2. Characteristics of maternal deaths in Menoufia 1981–1983

Characteristic	Maternal deaths *n* (%)
Education	
Illiterate women	294 (76·3)
Primary-school education	65 (17·0)
High-school education	26 (6·7)
Age (years)	
15–24	92 (23·8)
25–34	159 (41·3)
35–44	114 (29·6)
45–49	20 (5·2)
Parity	
0	4 (1·0)
1–3	181 (47·0)
4+	200 (51·9)
Place of death	
Home	204 (53·0)
Hospital	169 (43·9)
Other	12 (3·1)
Time of death	
During pregnancy	46 (11·9)
During labour	112 (29·1)
Postpartum	227 (59·0)
Total	385 100·0

than patients with antepartum haemorrhage. Most of the women with antepartum haemorrhage sought medical advice because of symptoms, but most of those with postpartum haemorrhage did not summon medical help. This may reflect a false sense of security in that the main event, delivery of the child, has apparently been completed satisfactorily. Postpartum haemorrhage is often sudden and severe and most of these deaths were home deliveries with the known difficulties in obtaining emergency medical help.

Sepsis. Although records indicated that all of these women received antibiotics (either in hospital or at home), postpartum sepsis accounted for 44 deaths (18%). The availability of a large array of recent and potent antibiotics did not help to diminish death from sepsis. The medical community in Egyptian villages should recognize that antibiotics alone are not sufficient against infection. Anaemia, malnutrition and poor hygiene contribute by diminishing the patients' resistance to sepsis. Lack of aseptic techniques during delivery (e.g in 'daya' deliveries) is an important cause of postpartum sepsis.

Pre-eclampsia and eclampsia. Hypertensive diseases of pregnancy accounted for 38 maternal deaths, being the third most common cause of direct obstetric deaths. Of these 38 deaths, 16 were associated with eclamptic fits. This high frequency of eclampsia is another strong indication of lack of antenatal care.

Caesarean section. There were 34 (14%) maternal deaths associated with caesarean section. The indications for section were: antepartum haemorrhage (10), obstructed labour (9), eclampsia (5), multiple pregnancy (2), diabetes mellitus (2), pre-eclampsia (1), uterine rupture (2), intrauterine fetal death (2), unknown (1). There was a preponderance of women of high parity in this group of maternal deaths, 18 of them had more than four previous deliveries. This indicates that women of high parity are more frequently exposed to the risks of surgical intervention because of hypertension, diabetes, larger babies and abnormal presentations and they should receive prenatal care and be booked well in advance for hospital delivery. Nine of the women who died had had between two and four previous deliveries which are usually the safest (Beazley 1986). If proper antenatal care had been provided in this subgroup there would have been fewer emergency caesarean sections, and elective section, a safer approach than emergency section, could have been performed.

Obstructed labour. Obstructed labour is a serious primary complication which does not itself cause death but leads to fatal complications including haemorrhage, ruptured uterus, dehydration and infection. There were 19 (8% of direct obstetric deaths) women who had prolonged obstructed labour. Of these, nine were managed by caesarean section while the other 10 were managed in other ways. Although information on the obstetric conditions was not clear, caesarean section would have seemed more appropriate. Four patients died at home with very little or no obstetric management. The other 15 patients died in hospital. These patients were late referrals and the seriousness of their condition is indicated by the fact that 12 died within 6 h of admission. The other three patients died within 2 days of admission. Causes of death in this group were either complications of ruptured uterus, haemorrhage, anaesthesia, or severe infection and septicaemia.

Abortion-related deaths. There were 21 maternal deaths due to abortion or miscarriage (Table 1). Induced abortion, though illegal in Egypt, was performed in six women. In seven women miscarriage occurred spontaneously. In the remaining eight maternal deaths it was not possible to determine whether the abortion was spontaneous or induced. Haemorrhage was the most common cause of death associated with abortion, followed by sepsis.

Indirect obstetric causes

There were 102 maternal deaths due to indirect obstetric causes (Table 1), and rheumatic heart disease was the main cause accounting for 36 (35%) maternal deaths.

Discussion

Many of the maternal deaths occurring in Menoufia could have been prevented had people made use of the available medical facilities for antenatal care and hospital deliveries rather than depending on the traditional midwives. Many of the deaths due to haemorrhage and sepsis could have been avoided had the deliveries occurred in hospitals with drugs and blood transfusions available.

Formal education is an important factor in the reduction of maternal mortality (Harrison 1985). Only 6·7% of the maternal deaths had had a high-school education and 76·3% were illiterate. Information and health education on the importance of antenatal care and hospital deliveries may be easily achieved through messages especially designed for uneducated people through the national communication media.

Although in Menoufia every health unit has one or two physicians, reluctance to attend health units may be explained by the fact that health unit doctors are usually young, inexperienced and are serving there for only 1 or 2 years. Doctors working in the villages are not usually there out of choice, but because it is an assignment they have to fulfill before they can start their graduate studies and plan for their future careers. This may explain why the villagers are reluctant to attend the health units and why the doctors do not exert an effort to win the confidence of the villagers.

Maternal death in women who are readily identifiable as being at high risk could have been prevented had the women used contraception to plan their families (fewer than 3% of the women who died from complications of pregnancy had ever used contraception). Indeed, more than half the maternal deaths in Menoufia occurred in women who had had four or more previous deliveries. Great strides can be made in reducing maternal mortality in Egypt by reducing fertility through voluntary contraception. If one weighs the benefits and risks of contraception, the benefits far exceed the risks in spite of less than optimal medical supervision (Cates 1980; Speroff *et al.* 1983).

As this was a retrospective study with no hospital death reports, it was difficult to determine avoidable factors, but we feel that a large percentage of these deaths could have been avoided. Zake (1982) reported avoidable factors in 70–80% of the deaths in Uganda; Moir (1964) and Borazjani *et al.* (1978) reported the corresponding values of 42·5% for England and Wales and 57·2% for South Iran respectively.

Although maternal mortality in Menoufia compares favourably with that in other developing countries, it is much higher than in the developed world. Augensen & Bergsjo (1984) reported 7·2 deaths/100 000 livebirths in Nordic countries, and the corresponding rate of 190 in Menoufia was 26 times higher than this. The reasons for this large difference include: (1) Communication and transport difficulties limited the utilization of government ambulances and hospitals. (2) Poverty and illiteracy of villagers and their preferences for home deliveries. (3) Most of the deliveries were performed by dayas who lack proper training.

The clinical causes of death in Menoufia are consistent with those reported from other developing countries. In Uganda, infection, haemorrhage and ruptured uterus were the three main causes of maternal death (Zake 1982). In England and Wales, on the other hand, pulmonary embolism and hypertension were the leading causes, followed by haemorrhage (Chamberlain 1983). Nevertheless, it has been estimated that nearly all (89%) of the deaths from pre-eclampsia and 62% of those from eclampsia are preventable (Davey 1986).

Many of the deaths in Menoufia, including 63% of those involving caesarean section and 80% of those with obstructed labour, occurred within 6 h of admission. Late referral of the patients contributes greatly to this, but other contributing factors are inadequate hospital facilities and physicians inexperienced in the management of obstetric emergencies. Senior obstetric and anaesthetic staff should be more involved in managing such emergency admissions.

Recommendations

We feel that great strides could be made in reducing maternal mortality if these recommendations were followed.

(1) The first priority is to improve utilization of existing facilities by improving the quality of services offered and by educating women in the importance of antenatal care, hospital deliveries and family planning.

(2) All efforts should be made to increase the proportion of hospital deliveries. In the meantime, training and supervision of traditional birth attendants is necessary.

(3) Hospital care must be improved both by continuing education for obstetricians and anaesthetists and by upgrading hospital facilities, such as intensive care, blood supplies and laboratory services. Often this is a question of good management and organization rather than additional expense.

(4) Different levels of health services (MCH centres with their birth attendant teams, rural health units, family planning clinics, local and district hospitals) must operate as an integrated team.

(5) A feasible system of confidential enquiries must be developed.

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The pathogenesis of genitourinary prolapse and stress incontinence of urine. A histological and histochemical study

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Summary. Histological and histochemical analysis of biopsy samples of pubococcygeus muscle obtained from asymptomatic women and from women with stress incontinence of urine, with or without genitourinary prolapse, have been compared. In the asymptomatic women both age and parity appeared to be related to the morphological features of the samples and in particular those obtained from the posterior part of the pubococcygeus. In the symptomatic women there was a significant increase in the number of muscle fibres showing pathological damage which were obtained from the posterior part of the pelvic floor. The range of diameters of both Type I and Type II fibres obtained from this region was significantly different between symptomatic and asymptomatic women. These findings may be attributable to partial denervation of the pelvic floor in patients with urinary stress incontinence with or without genital tract prolapse.

Previous histochemical studies of biopsy samples of the external anal sphincter, puborectalis and levator ani muscles (Parks *et al.* 1977; Beersiek *et al.* 1979) have suggested that partial denervation of the pelvic floor occurs in patients with rectal prolapse and faecal incontinence. The possibility therefore exists that damage to the innervation of the pelvic floor may also be a factor in the aetiology of urinary stress incontinence and genital tract prolapse. The purpose of the present study was to determine the structural and histochemical characteristics of striated muscle obtained from selected parts of the pubococcygeus in women with normal urinary control and no prolapse and to compare these findings with those from patients with stress incontinence of urine or genital tract prolapse or both.

Patients and methods

In the present investigation 46 biopsy samples (Table 1) have been examined from the medial aspects of the pubococcygeus; 19 of them were obtained from 11 women without stress incontinence or genital tract prolapse during surgery for benign pelvic disease In 10 of these patients single-fibre electromyography (SFEMG) recordings were obtained and the motor unit fibre densities were found to range from 1·2 to 1·6 (normal range 1·2–1·8; Smith *et al.* (1989)). The other 27 samples were obtained from 16 women with unequivocal evidence of stress incontinence of urine and, in all but two, genital tract prolapse. In these 16 women the results of SFEMG were all abnormal and showed motor unit fibre density of ≥2·0. In the symptomatic

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Table 1. Histology and source of pubococcygeus muscle biopsies in the study

	Asymptomatic women (n = 11)		Symptomatic women (n = 16)	
Characteristic	Anterior pubococcygeus	Posterior pubococcygeus	Anterior pubococcygeus	Posterior pubococcygeus
No. of women	6	5	9	7
No. of parous women	0	3	9	7
Age range (years)	19–52	19–75	42–69	39–79
No of biopsy samples	11	8	14	13
Proportion of pathological cells (%)	≤3	8 (3)	3–16 (range)	17 (3)**
Proportion of Type II fibres (%)	33 (5)	24 (6)	39 (5)	10 (3) (n = 10)
Fibre diameter (μm)				
Type I	45 (2)	43 (4)	46 (2)	57 (2)*
Type II	43 (3)	49 (2)	40 (1)	55 (6)

Significantly different between asymptomatic and symptomatic women * $P<0{\cdot}01$, ** $P<0{\cdot}05$.
Results are means (SE) values where appropriate

group, tissue was obtained from the pelvic floor during the surgical treatment of their condition. The site of muscle biopsies is shown in Fig.1. Biopsies of approximately 5 mm^3 were obtained by grasping a portion of muscle with a single-tooth volsellum and severing the elevated portion from the muscle bulk with a new number 11 Bard-Parker blade. This rarely caused bleeding. The muscle sheath was closed with a single catgut suture.

Where more than one biopsy sample was obtained from anterior and/or posterior parts of the pubococcygeus in the same patient, the data for each site were combined to give the mean value. These means were used in subsequent data analysis.

Preparation of tissue samples

Biopsy samples were orientated so as to provide transverse sections of muscle fibres, mounted on cork discs and rapidly frozen in dichlorodifluoroethane cooled in liquid nitrogen. Cryostat sections, each 10 μm in thickness, were processed to demonstrate either histological structure using a trichrome technique or tissue actomyosin ATPase activity (Guth & Samaha 1969).

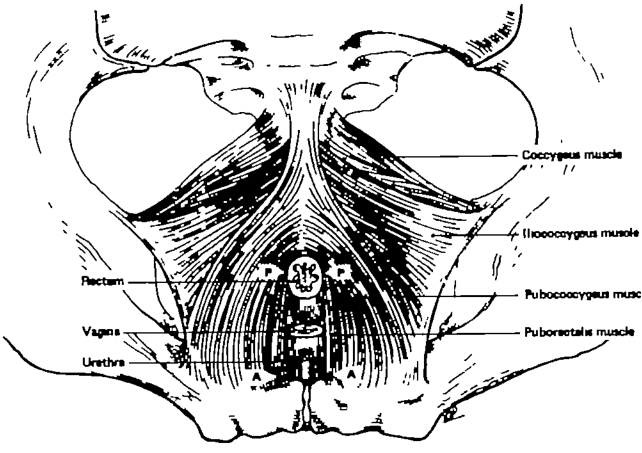

Fig. 1. The pelvic floor from above. The anterior and posterior biopsy sites are labelled A and P respectively.

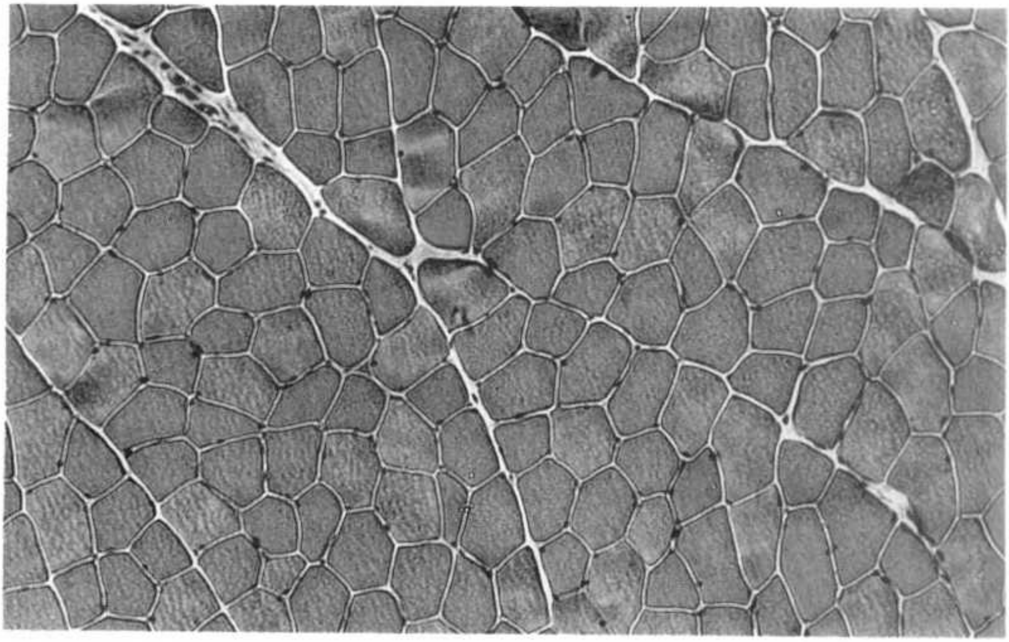

Fig. 2. Photomicrograph of striated muscle cells obtained from the anterior part of the pubococcygeus in an asymptomatic woman. Massons Trichrome ×106.

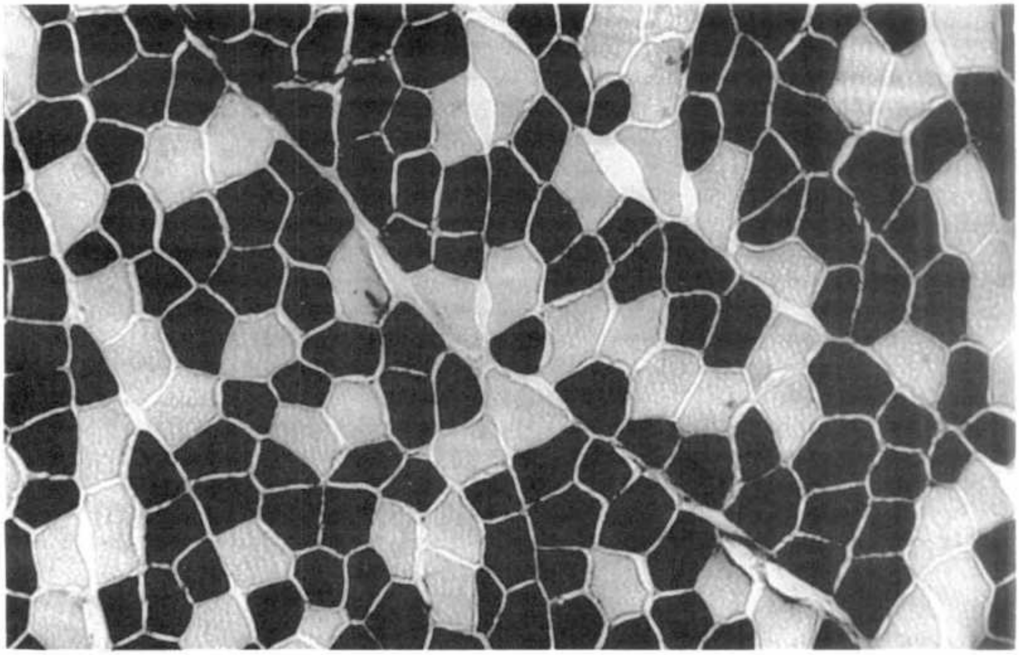

Fig. 3. Adjacent section to that illustrated in Fig. 2 showing both Type I (black) and Type II (white) fibres. Actomyosin ATPase preparation ×106.

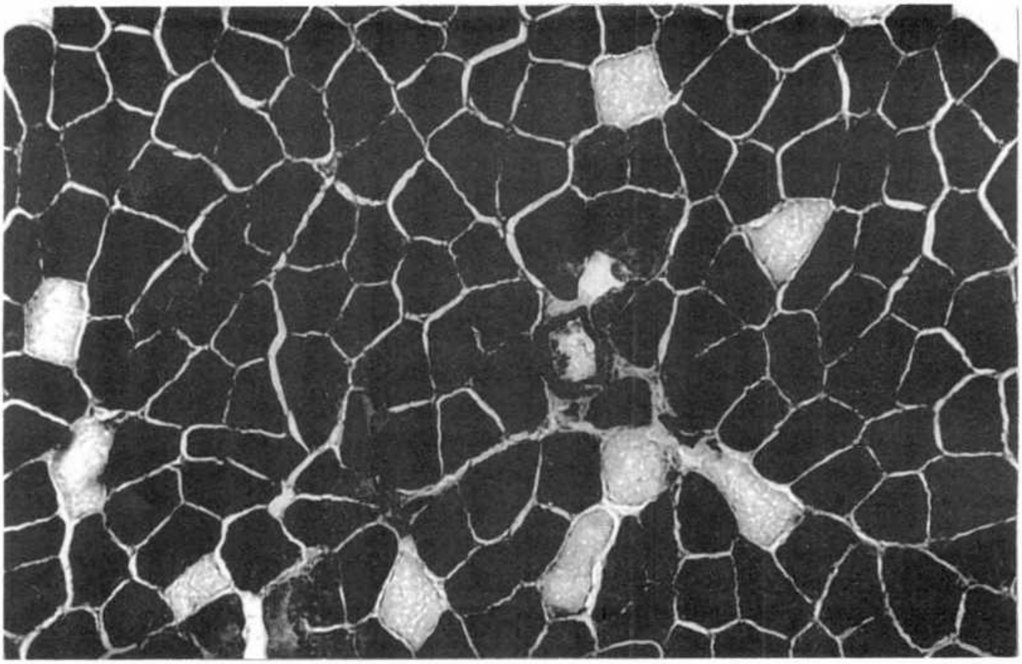

Fig. 4. Section showing adjacent Type I fibres grouped together (obtained from the same biopsy sample illustrated in Figs 2 & 3). Actomyosin ATPase preparation ×106.

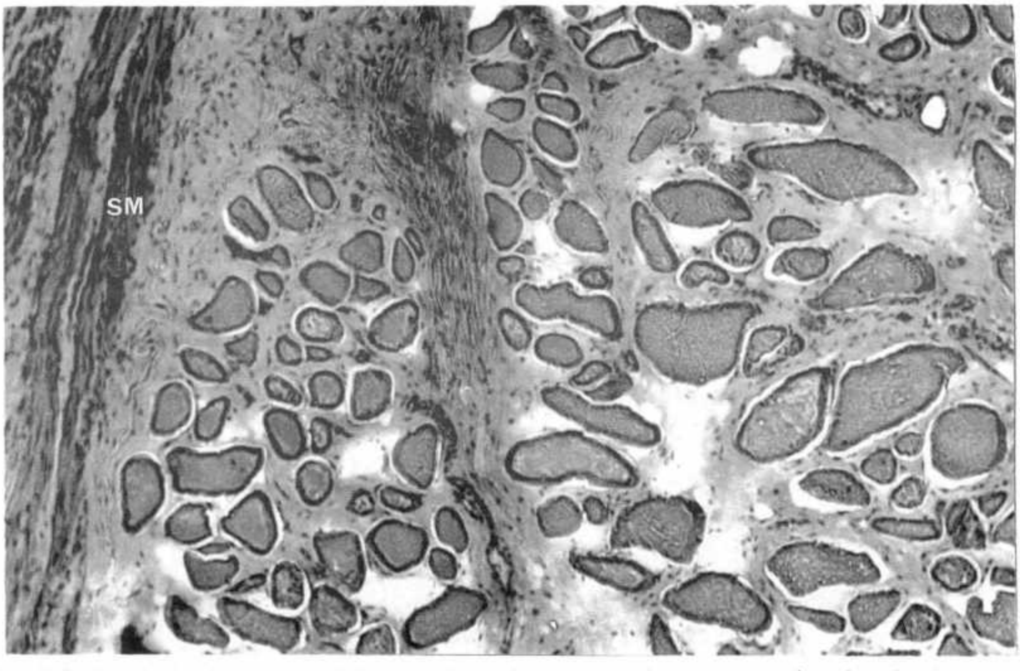

Fig. 5. Section obtained from the posterior part of the pubococcygeus of an asymptomatic patient showing loosely packed striated muscle fibres associated with bundles of smooth muscle (SM). Massons Trichrome ×106.

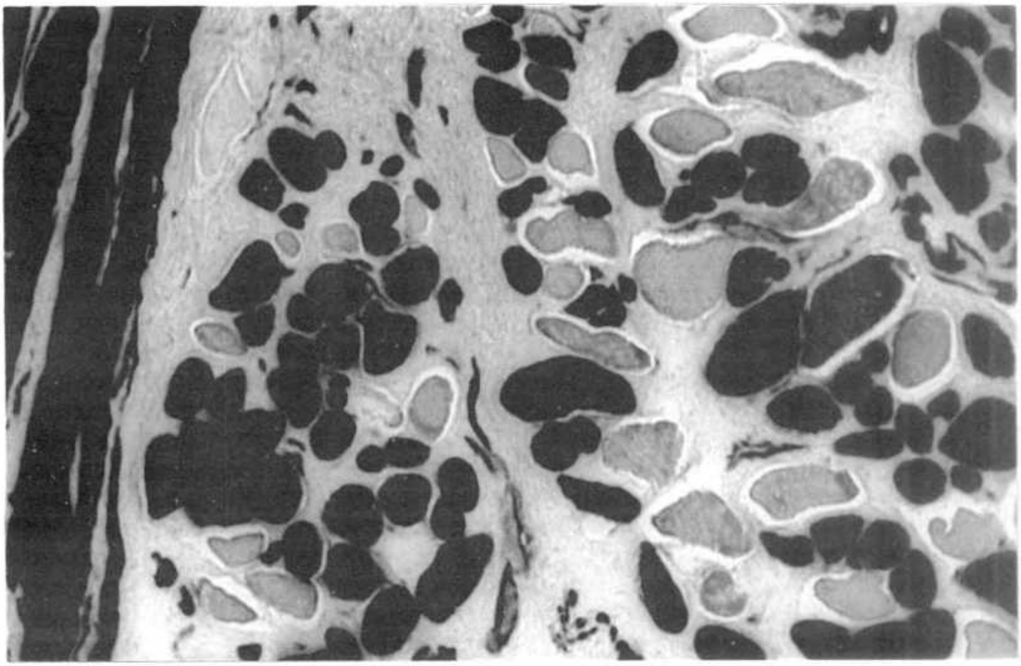

Fig. 6. Adjacent section to that illustrated in Fig. 5 showing a mixture of Type I and Type II fibres. Actomyosin ATPase preparation ×106.

Histology

Sections comprising a minimum of 500 fibres were examined from each biopsy sample and the percentage of muscle cells showing histological evidence of pathological change (i.e. central nucleation, muscle fibre splitting or cell necrosis) was recorded.

Size, proportions and distribution of fibre types

To standardize measurements, analysis of fibres processed using the method for actomyosin ATPase was performed on material processed at pH 4·35. Random non-overlapping fields obtained from each section were photographed at standard magnification and photographic prints prepared. The size of each fibre was calculated by measurement of the narrowest diameter passing through the estimated centre of gravity (Dubowitz & Brooke 1973). The proportion of fibre types (Type I—slow; Type II—fast) was calculated and the method devised by Jennekens *et al.* (1971) used to determine the spatial arrangement of fibre types.

Statistical analysis

All the data were checked with Filliben's method (Wainwright & Gilbert 1981) for normal distribution. Groups of all normally distributed

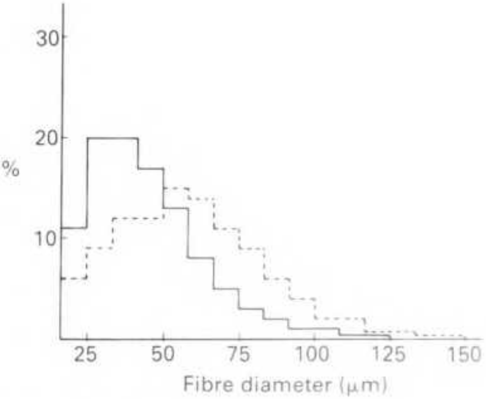

Fig. 7. Distribution of Type I fibres in biopsy samples from the posterior part of the pubococcygeus in asymptomatic (———) and symptomatic (– – – –) patients. Significantly different at the 1% level (Kolmogorov–Smirnov).

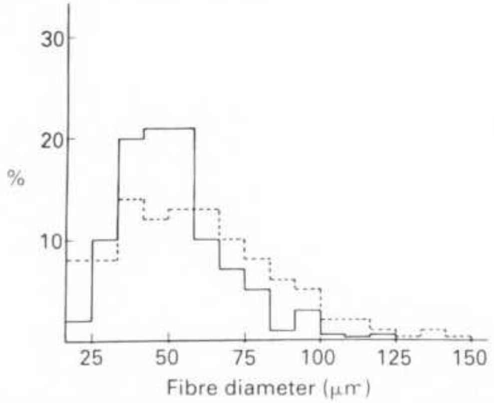

Fig. 8. Distribution of Type II fibres in biopsy samples from the posterior part of the pubococcygeus in asymptomatic (———) and symptomatic (– – – –) patients. Significantly different at the 2% level (Kolmogorov–Smirnov).

data were compared using Student's *t*-test. Where comparisons were made between either normally distributed groups and non-normally distributed groups or between all non-normally distributed groups, the Mann–Whitney *U*-test was used. Comparisons of frequency distribution were made with the Kolmogorov–Smirnov test.

Results

(1) Women with normal urinary control and no prolapse

(A) Anterior pubococcygeus

Histology. Histologically samples of the anterior part of the pubococcygeus consisted of closely packed striated muscle fibres arranged into fascicles by connective tissue septa (Fig. 2). A smooth muscle component was absent from this part of the pubococcygeus and the proportions of striated cells showing pathological characteristics were 3% or less (considered by Schwartz *et al.* (1976) to be within the normal range).

Proportion and distribution of fibre types. Specimens from the anterior part of the pubococcygeus consisted of a mixture of Type I and Type II fibres (Fig. 3). The mean proportion of Type II fibres was 33% (SE 5; range 21–62). In some parts of the biopsy samples, several adjacent cells were each of the same fibre type (Fig. 4).

Fibre diameter. Type II fibres had a mean narrow diameter 43 μm (SE 3), whereas the mean value for Type I fibres was 45 μm (SE 2). Individual

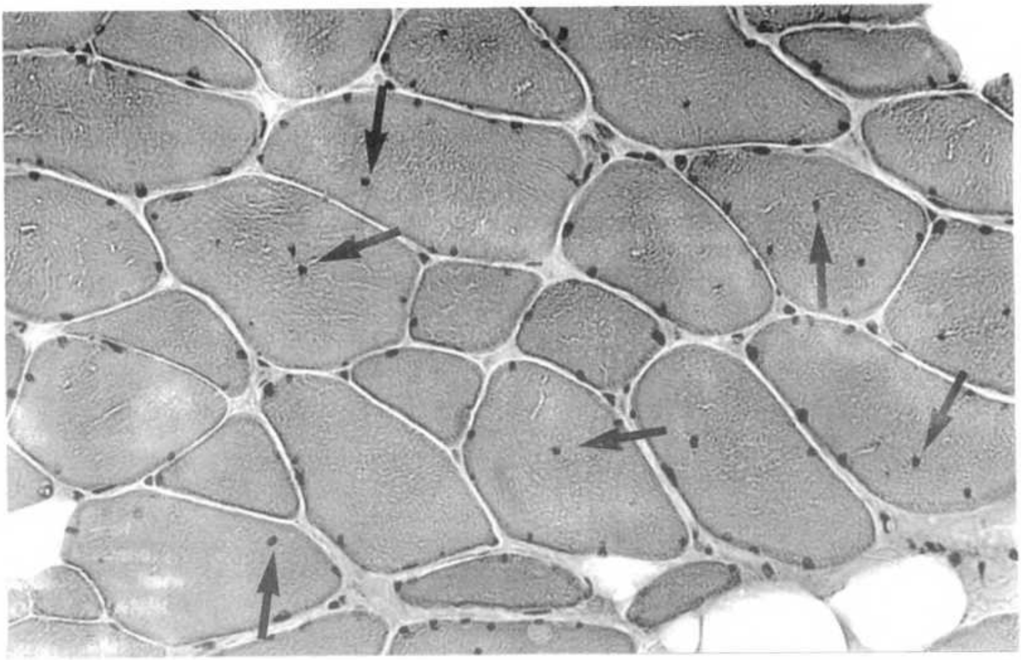

Fig. 9. Section from the posterior part of the pubococcygeus in a symptomatic patient showing striated muscle cells with centrally located nuclei (arrows). Massons trichrome ×212.

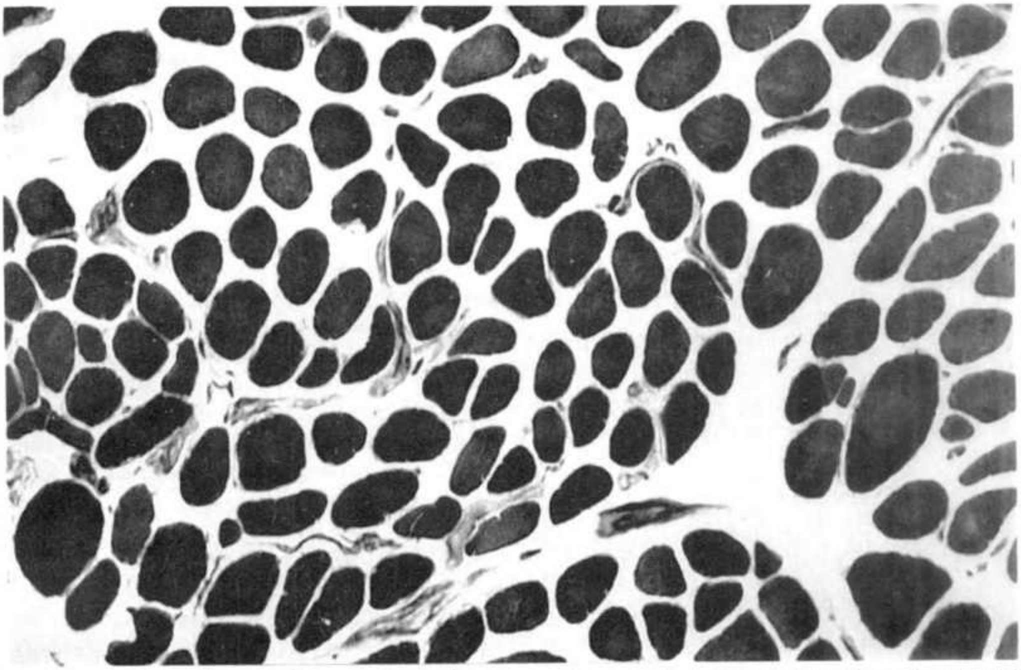

Fig. 10. Section from the posterior part of the pubococcygeus in a symptomatic patient showing striated muscle consisting exclusively of Type I fibres. Actomyosin ATPase preparation ×106.

Type I and Type II fibre diameters ranged in size from 17 to 90 μm.

(B) Posterior pubococcygeus

Histology. Samples obtained from the posterior part of the pubococcygeus contained striated muscle fibre separated into fascicles by relatively large amounts of connective tissue. In addition, smooth muscle bundles were frequently observed amongst the striated muscle component (Fig. 5). Although the difference was not statistically significant, centrally located nuclei occurred relatively often in striated muscle with a mean of 8% (SE 3; range 0·5–19). This histological appearance was particularly evident in the older parous women.

Proportion and distribution of fibre types. All biopsies contained a mixture of both Type I and Type II fibres (Fig. 6). The mean proportion of Type II fibres was 24% (SE 6; range 11–63). Unlike anterior biopsies, fibres of the same type were not associated in groups in samples from the posterior portion of pubococcygeus.

Fibre diameter. The Type II fibres had a mean diameter of 49 μm (SE 2) and the value for Type I fibres was 43 μm (SE 4). A range of 17–125 μm was obtained from the total of striated fibres examined (Figs 7 & 8).

(2) Symptomatic women

(A) Anterior pubococcygeus

Histology. The arrangement of striated muscle was indistinguishable from that in control samples. However, in four biopsy specimens obtained from three patients, histological evidence of pathological change (central nucleation) was evident in more than 3% (3·5–16%) of the fibre population.

Proportion and distribution of fibre types. The proportion of Type II fibres in biopsy samples of the anterior part of pubococcygeus was 39% (SE 5; range 20–58), not significantly different from values in asymptomatic women.

Fibre diameter. The Type II fibres had a mean diameter of 40 μm (SE1; range 17–100). The mean diameter of Type I fibres was 46 μm (SE 2; range 17–125). The fibre diameters were not significantly different from those in asymptomatic women (Mann–Whitney *U*-test).

P, 25, 385

(B) Posterior pubococcygeus

Histology. In all biopsy samples obtained from the posterior part of the pubococcygeus a significant proportion of fibres demonstrated pathological characteristics (Fig. 9). A mean of 17% (SE 3) of the fibres possessed centrally located nuclei (compared with asymptomatic patients significant at 5% level—Mann–Whitney *U*-test), and split and necrotic fibres were frequently observed.

Proportion and distribution of fibre types. Three biopsy samples, each obtained from different symptomatic patients, consisted solely of Type I fibres (Fig. 10). In the remaining samples the mean proportion of Type II fibres was 10% (SE 3; range 3–26). The distribution of fibre types in these samples was similar to that in asymptomatic patients

Fibre diameter. Type II fibres had a mean diameter of 55 μm (SE 6; range 17–150) and the mean value for Type I fibres was 57 μm (SE 2; range 17–150) (Figs 7 & 8). Although there was no significant difference between the symptomatic and asymptomatic women in the diameter of Type II fibres, the diameter of Type I fibres was significantly greater in the symptomatic women (P<0·01; Student's t-test) In addition the frequency distribution of fibre diameter for both fibre types was significantly different between the symptomatic and asymptomatic women (Type I fibre P<0·01, Type II fibre P<0·02, Kolmogorov–Smirnov).

Discussion

One of the aims of the present study was to provide histological and histochemical control data on those parts of the pubococcygeus which are related either to the urethra or to the anorectal region. The results have revealed subtle but nevertheless important differences between the anterior and posterior parts of the pubococcygeus which must be considered when evidence is sought for pathological alteration of pelvic floor musculature and its innervation. Histochemical evidence, supporting the occurrence of partial denervation and subsequent reinnervation of striated muscle, is provided by the clustering together of fibres all of the same type (Dubowitz 1970). In this context it is noteworthy that such fibre groupings have been observed in the present study in some of the biopsy samples from the anterior part of the puboccocygeus in asymptomatic women. Whilst it may be that these findings represent otherwise unsuspected alteration in the innervation of this part of the pubococcygeus, the absence of symptoms referrable to the pelvic floor musculature, the paucity of histological evidence of muscle fibre pathology and the normal values of SFEMG recorded from these women support the view that this apparent grouping of fibre types is probably representative of normal variation. In addition, our findings in biopsies from the posterior component of the pubococcygeus in asymptomatic women have revealed an association between the histological features and the age and parity of these women. Thus, increased occurrence of muscle fibres showing evidence of pathology is more likely in older parous women. This finding warrants further investigation since it may be that childbirth alters the structure of the pelvic floor even in asymptomatic women. Collectively, however, the results obtained from these patients raise uncertainty about the conclusions reached in previous studies (Parks *et al.* 1977; Beersiek *et al.* 1979) which have examined striated muscle from the levator ani.

However, significant differences in structure and histochemistry have been demonstrated between symptomatic and asymptomatic women in the striated muscle samples obtained from the posterior part of the pubococcygeus. The differences include hypertrophy of Type II fibres, increase in the proportion of Type I fibres and a significant increase in the proportion of muscle fibres which possess centrally located nuclei. These results are suggestive of local partial denervation accompanied by reinnervation. Further evidence of nerve fibre damage in symptomatic women is provided by the results of the SFEMG technique. Since these changes are confined to the posterior part of the pelvic floor the possibility exists that they may be caused by direct pressure of the fetal head during labour. Whatever the precise aetiology, the present results have shown that marked alteration of the striated muscle of the pubococcygeus occurs in women suffering from genital tract prolapse and urinary stress incontinence.

Acknowledgments

Permission to undertake this study was obtained from the ethics committee of St Mary's Hospital, Manchester. The patients gave informed consent. We are grateful for funding by the obstetric charity Birthright, to the consultant staff of St Mary's Hospital for their co-operation, and most of all to the patients who contributed to this work.

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The role of partial denervation of the pelvic floor in the aetiology of genitourinary prolapse and stress incontinence of urine. A neurophysiological study

A. R. B. SMITH, G. L. HOSKER, D. W. WARRELL

Summary. Single-fibre electromyography of the pubococcygeus muscle of the pelvic floor was performed in 69 asymptomatic women and 105 women with stress incontinence of urine or genitourinary prolapse or both. The results suggest that partial denervation of the pelvic floor with subsequent reinnervation is a normal accompaniment of ageing and is increased by childbirth. Women with stress incontinence of urine or genitourinary prolapse or both have a significant increase in denervation of the pelvic floor compared with asymptomatic women.

Clinically,women with genitourinary prolapse or stress incontinence of urine have a weaker pelvic floor muscle than normal women. A similar pelvic floor weakness has been observed in women with rectal prolapse and faecal incontinence. Muscle histochemistry and neurophysiological studies have shown that these patients have a partially denervated pelvic floor and external anal sphincter (Parks *et al.* 1977; Beersiek *et al.* 1979; Neill & Swash 1980). Histochemical studies of pelvic floor muscle biopsies from women with genitourinary prolapse and stress incontinence of urine have demonstrated evidence of muscle fibre damage (Gilpin *et al.* 1989).

This paper reports the results of a single-fibre electromyographic study of the pubococcygeus muscle of the pelvic floor in normal women and in women with stress incontinence of urine and genitourinary prolapse.

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Patients and methods

The study included 174 women, 69 had normal urinary control and no prolapse and the other 105 had stress urinary incontinence or genitourinary prolapse or both. The women with prolapse or stress incontinence were under investigation in the Urodynamic Unit at St Mary's Hospital. The women without urological symptoms were selected from women undergoing in-patient investigation for benign gynaecological disorders. All the women were assessed by general examination and pelvic examination and history. The diagnosis of genuine stress incontinence was established by the demonstration of stress incontinence and normal bladder function as assessed by retrograde provocative filling cystometry. Prolapse was assessed by clinical examination with a Sims speculum in the left lateral position. Descent of the anterior vaginal wall, posterior vaginal wall or cervix to the introitus at rest or with straining was classified as genitourinary prolapse.

Single-fibre electromyography (SFEMG)

The electrical field of a muscle fibre can be recorded as an action potential. The single-fibre electromyography needle electrode has a 25 μm diameter and can focus on the activity of a single muscle fibre. Other muscle fibres, firing synchronously and picked up by the electrode will have the same innervation. Denervation of muscle followed by reinnervation causes the ratio of muscle fibres to nerve fibres to increase so that up to eight action potentials may be recorded by a single needle electrode. When this is seen it is reliable evidence of partial denervation (Stalberg & Trontelj 1979). In practice, the average number of action potentials recorded from 20 different needle sites is taken and the ratio obtained is the motor unit fibre density. In this study the patient was investigated in the supine position. A balloon catheter was placed in the rectum (above the level of the pelvic floor) and filled with 50 ml air. A weighted cord of 150 g was attached to the catheter to apply traction to the pelvic floor so that increased muscle activity was required to retain the balloon. This increased muscle activity facilitated SFEMG recording. A ground electrode was applied to the right thigh to reduce electrical interference. A vaginal examination was performed with the right hand and the pubococcygeus muscle was located by palpation through the lateral vaginal wall. A Medelec SF 75 single-fibre needle electrode was held in the left hand and guided into the pubococcygeus muscle with the index finger of the right hand in the vagina. The length of the SF75 needle (7·5 cm) allowed the needle to be manipulated in the muscle from outside the vagina. The amplifier was set to SFEMG (filter 500 Hz–10 kHz). A sweep velocity of 2 ms/division was used and a signal delay unit positioned the triggered action potential in the middle of the oscilloscope screen. The threshold was altered when the electrode approached an action potential so that the oscilloscope would only be triggered by the maximum action potential.

The localization of action potentials was considerably aided by the audio signal which indicated the presence of nearby potentials often before they were displayed on the oscilloscope. A raster of five consecutive recordings was taken when a stable configuration was displayed on the oscilloscope. Any action potential appearing in an identical position on the 5-raster recording had to be originating from a muscle fibre which had the same innervation as the muscle fibre producing the trigger potential. Twenty different recordings were made in an area of muscle. This necessarily involved relocating the needle in the muscle.

Results

Nulliparous asymptomatic women

Measurements of fibre density from these 41 nulliparous women are given in Fig. 1. Fibre density increased significantly with age ($P<0{\cdot}00001$; linear regression) from 1·2 at 20 years to 1·6 at 77 years, this increase was 0·07 every 10 years.

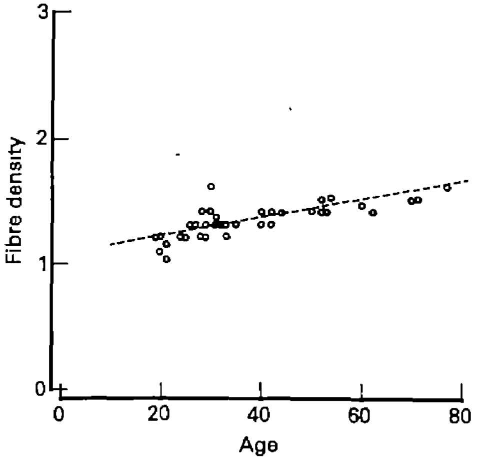

Fig. 1. Motor unit fibre density in the pelvic floor of nulliparous asymptomatic women according to age. The linear regression line has been calculated. Gradient 0·00670 (SE 0·00085) $P<0{\cdot}00001$.

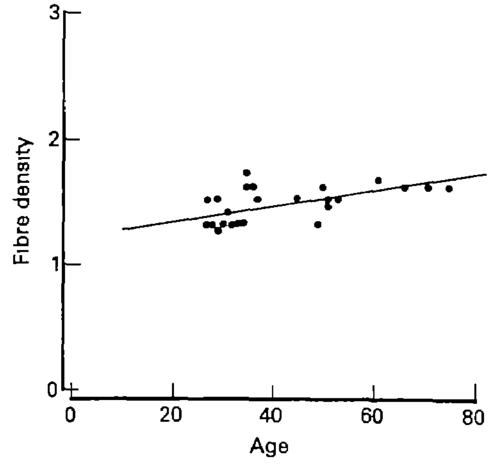

Fig. 2. Motor unit fibre density in the pelvic floor of asymptomatic parous women according to age. The linear regression line has been calculated. Gradient 0·00639 (SE 0·00161) $P=0{\cdot}00077$.

Parous asymptomatic women

Measurements of fibre density from these 28 parous women are given in Fig. 2. The fibre density increased significantly with age ($P = 0{\cdot}00077$; linear regression) from 1·4 at 26 years to 1·7 at 75 years, this increase was 0·06 every 10 years. Age for age the fibre density was greater in the parous than in the nulliparous asymptomatic women ($P = 0{\cdot}0001$; analysis of covariance). This difference age for age was approximately 0·1 and is illustrated in Fig. 3.

Women with stress incontinence of urine without genitourinary prolapse

Measurements of fibre density from the 28 women with stress incontinence but no genitourinary prolapse are given in Fig. 4. The fibre density increased significantly with age ($P = 0{\cdot}01046$; linear regression) from 1·7 at 22 years to 2·1 at 77 years, this increase was 0·08 every 10 years.

Age for age the fibre density in women with stress incontinence of urine but no prolapse was greater than in the normal parous women studied (analysis of covariance $P<0{\cdot}00001$).

Women with genitourinary prolapse with or without stress incontinence

Measurements of fibre density from 61 women with stress incontinence and prolapse and 16 women with prolapse alone showed no change in fibre density with age in either of the groups ($P = 0{\cdot}524$ and $P = 0{\cdot}886$ respectively; linear regression). There was no statistically significant difference in the mean fibre density between the two groups [stress incontinence with prolapse: 2·1 (SD 0·4), prolapse alone: 2·1 (SD 0·3), $P = 0{\cdot}778$, Mann–Whitney *U*-test]. The fibre density of these two groups is illustrated in Fig. 5. The fibre density in both groups was significantly greater than that in asymptomatic parous women ($P<0{\cdot}00001$; Wilcoxon matched-pairs signed-rank test). To account for the age dependency of the fibre density in the asymptomatic women, the fibre density of each woman with symptoms was compared with the fibre density obtained from the regression line for an asymptomatic parous woman of corresponding age.

By a similar analysis, there was no significant difference in fibre density between the women with stress incontinence but no prolapse and these two groups of women ($P = 0{\cdot}54$; Wilcoxon matched-pairs signed-rank tests).

Clinical correlations

The history and examination of the women revealed the following clinical correlations related to the development of stress incontinence and prolapse (Table 1).

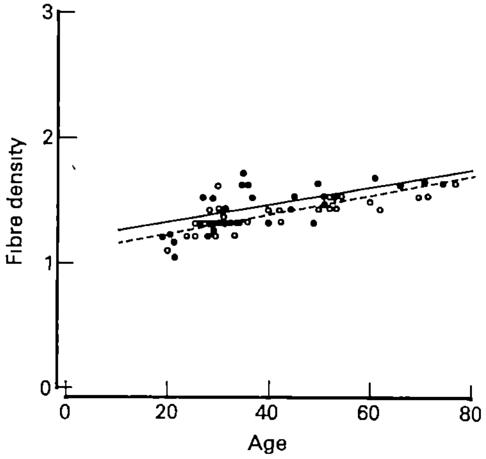

Fig. 3. Motor unit fibre density in the pelvic floor of nulliparous (O) and parous (●) asymptomatic women according to age The lines for nulliparous (– – – –) and parous (————) women are shown.

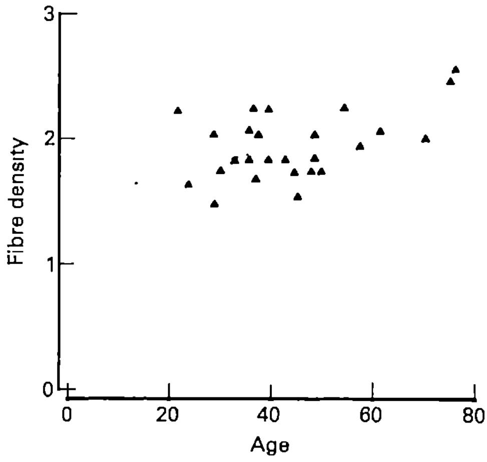

Fig. 4. Motor unit fibre density in the pelvic floor of parous women with stress incontinence but no prolapse according to age The linear regression line has been calculated. Gradient 0·00847 (SE 0·00308) $P = 0{\cdot}01046$.

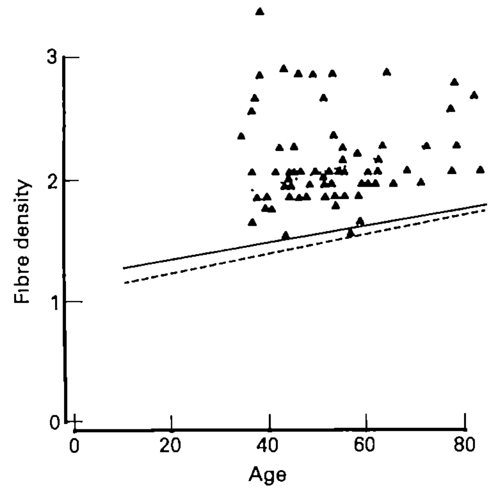

Fig. 5. Motor unit fibre density in the pelvic floor of women with prolapse, with or without stress incontinence. The regression lines for asymptomatic nulliparous (– – – –) and parous (————) women, and women with stress incontinence alone (······ ···) are shown.

Age and oestrogen deficiency. Women with prolapse alone were significantly older than women with stress incontinence ($P = 0{\cdot}00005$; Student's t-test). In the menopausal women a greater proportion of the symptomatic women had signs of oestrogen deficiency such as atrophic vaginitis than the asymptomatic women. However, the difference was not statistically significant.

Obesity. This was measured as the body-mass index (BMI) = weight (kg)/height^2 (m^2). Women in the symptomatic groups were significantly more obese than the asymptomatic women ($P<0{\cdot}00001$; Student's t-test).

Family history. A positive family history (incontinence in a close relative) was noted more often in women with symptoms than in the asymptomatic women. However, the difference was not statistically significant.

Obstetric history. There was no statistically significant difference in parity ($P = 0{\cdot}66$; Mann–Whitney U-test) or heaviest infant birthweight between the women with symptoms and the asymptomatic parous women. However, the fact that only one of the women with prolapse and stress incontinence was nulliparous highlights the important role of parity in the aetiology of denervation injury. All women were questioned about perineal injury during childbirth. The clarity of recall was variable and the results have to be interpreted appropriately but they implied that women who have had an episiotomy during delivery (without a tear) were less likely to develop stress incontinence of urine or prolapse than women who either had a tear or no sutures whatsoever.

Discussion

These results show that the pelvic floor is partially denervated in women with stress

Table 1. Characteristics of the women in the study groups

	Asymptomatic		Symptomatic		
Characteristic	Nulliparous (n = 41)	Parous (n = 28)	Stress incontinence only (n = 28)	Prolapse only (n = 16)	Stress incontinence and prolapse (n = 61)
Age (years) mean (SD)	38 (15)	41 (14)	44 (15)	65 (13)	51 (11)
Body-mass index (kg/m^2) mean SD	21 8 (1·9)	22·4 (1·7)	23·8 (3·4)	24·9 (2·3)	24·2 (2·4)
Menopausal n (%)	11 (27)	6 (21)	9 (32)	14 (88)	30 (50)
Vaginal atrophy n (%)	5 (12)	3 (12)	6 (21)	11 (69)	21 (53)
Family history of incontinence n (%)	2 (5)	1 (4)	4 (14)	1 (6)	6 (10)
Parity mean (SD)	—	2·6 (1·5)	2·3 (1·1)	2·6 (1·2)	3·1 (2·2)
Heaviest infant birthweight (kg) mean (SD)	—	3·24 (0·57)	3·64 (0·62)	3·53 (0·87)	3·57 (0·74)
No sutures n (%)		10 (36)	11 (39)	8 (50)	29 (48)
Tears n (%)		10 (36)	13 (46)	5 (31)	28 (46)
Episiotomy n (%)		8 (29)	2 (7)	3 (19)	3 (5)

incontinence of urine or genital tract prolapse or both. The gradual increase in denervation of the striated muscle of the pelvic floor with age in nulliparous women is in accordance with the findings in other striated muscles in the body (Stalberg & Thiele 1975). Childbearing appears, in some clinically normal women, to increase the pelvic floor denervation, but not to the levels seen in women with stress incontinence or genitourinary prolapse.

There was no correlation between the number of pregnancies or the heaviest baby weight and the degree of pelvic floor denervation. The reduced occurrence of stress incontinence or prolapse in women who had an episiotomy and no perineal tear supports the claim of reduced pelvic floor injury when episiotomy is performed.

The pelvic floor denervation seen in women with stress incontinence of urine and no prolapse may be of relevance in the aetiology of the condition for it has been shown that the transmission of cough-induced pressure changes to the urethra is reduced in women with stress incontinence (Beck & Maughan 1964). It may be that a denervated pelvic floor provides poor urethral support and results in diminished transmission of intra-abdominal pressure to the proximal urethra.

Our finding of partial denervation and consequent weakening of the pelvic floor in prolapse of the pelvic viscera contributes to the old argument whether prolapse is due to muscle or fascial damage and provides an explanation of the findings of the work of Berglas & Rubin (1953) on levator myography. They report that in healthy nulliparous women in the erect position the vaginal axis is close to horizontal and that the pelvic viscera are supported by the levator plate. In women with genital tract prolapse the levator plate sags inclining the axis of the vagina towards the vertical and widening the introitus. The mechanical effect of this change is to increase the strain on the so-called fascial supports of the pelvic viscera. This concept does not preclude fascial damage as a factor in prolapse but does explain how pelvic floor muscle damage may adversely affect the position of a pelvic viscus immediately supported by smooth muscle, blood vessels, collagen and elastic tissue.

The clinical relevance of this study in relation to reconstructive surgery for genitourinary prolapse and stress incontinence concerns the approach to the surgery, for in a vaginal approach the support provided relies on the integrity of the remaining pelvic floor. In women in whom the pelvic floor is very weak, or in young women who will inevitably develop further age-related denervation weakness, reconstructive surgery may be better performed abdominally for this approach enables the pelvic floor and fascia to be attached to the bony pelvis giving a fixed support which should not diminish over the ensuing years.

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The role of pudendal nerve damage in the aetiology of genuine stress incontinence in women

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Summary. Conduction was studied in the terminal branches of the pudendal nerve in 42 women with normal urinary control and 87 women with stress incontinence of urine, genitourinary prolapse, or both. Women with stress incontinence of urine had delayed conduction to both the striated urethral muscle and the pelvic floor muscle, indicative of denervation injury. Women with normal urinary control and genitourinary prolapse had similar conduction times to the urethral sphincter striated muscle as normal women but clear evidence of denervation damage to the pelvic floor.

Histochemical studies of pelvic floor muscle biopsies and pelvic floor single-fibre electromyography have demonstrated evidence of muscle fibre damage in the pelvic floor of women suffering from genital tract prolapse or stress incontinence of urine (Gilpin *et al.* 1989; Smith *et al.* 1989). Nerve damage with resultant pelvic floor muscle weakness is a common finding in women with stress incontinence of urine. These studies raised the question of whether selective damage to the nerve supply of the striated muscle of the urethral sphincter produces a muscle weakness resulting in stress incontinence of urine. Urethral sphincter denervation in women with stress incontinence would explain the frequent, but not invariable, association of stress incontinence with genital tract prolapse since both the pelvic floor muscles and the striated urethral sphincter are innervated by terminal branches of the pudendal nerve. Frankson & Petersen (1956) found urethral sphincter denervation in two out of eight women with stress incontinence of urine. Vereecken *et al.* (1981) studied 91 women with stress incontinence and showed electromyographical abnormalities of the striated urethral sphincter in 78% Anderson (1984) performed single-fibre electromyography in the external anal sphincter in women with stress incontinence of urine (but normal control of faeces) and noted evidence of partial denervation. Snooks & Swash (1984) recorded the nerve conduction to the striated urethral sphincter and found delayed conduction, indicative of partial denervation.

This study of nerve conduction in the terminal branches of the pudendal nerve was designed to investigate the aetiology of the urethral sphincter weakness seen in women with stress incontinence of urine and to determine whether selective damage to the terminal branches of the pudendal nerve produces selective muscle weakness in the external anal sphincter, pelvic floor and external urethral sphincter muscles.

Patients and methods

The study included 129 women of whom 42 had normal urinary control and no prolapse and the other 87 had stress incontinence or genitourinary prolapse or both. The conduction time to the

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urethra and anal sphincter was measured in all patients. The conduction time measurement to the pubococcygeus muscle was introduced during the study and was performed in 26 normal women and 60 symptomatic patients.

The women with normal control were volunteers attending hospital with unrelated disorders. The women with symptoms of prolapse and stress incontinence had been referred to the gynaecological clinic by their general practitioners. Women were assessed by history and examination, uroflowmetry, provocative cystometry, urethral profilometry and cystoscopy. The patients with stress incontinence were classified as being with or without genitourinary prolapse. Women with prolapse and no stress incontinence were also studied. Prolapse was assessed by the same examiner (A.R.B.S.) throughout the study by clinical examination with a Sims speculum in the left lateral position. Descent of the anterior vaginal wall, posterior vaginal wall or uterus to the introitus at rest or with straining was classified as prolapse. Evidence of detrusor instability at cystometry led to exclusion from the study. Stress incontinence was diagnosed by the demonstration of stress incontinence and normal cystometry.

The time taken for a muscle to respond to a pudendal nerve stimulus was measured in the external anal sphincter, pubococcygeus muscle and external urethral sphincter by stimulation of the pudendal nerve on each side. Conduction in the terminal branches of the pudendal nerve was measured using the technique devised by Kiff & Swash (1984) and modified by Snooks & Swash (1984). In this study vaginal surface electrodes were developed to pick up the response of the pubococcygeus muscle by modification of a cuffed endotracheal tube. The patient was placed in the left lateral position with a ground electrode on the right thigh. The external urethral meatus was cleansed and a sterile Dantec urethral ring electrode mounted on a Foley catheter was positioned in the urethra. The modified endotracheal tube cuff (Fig. 1) was then placed in the vagina and the cuff inflated to approximate the surface electrodes to the pubococcygeus muscle in the lateral vaginal wall. A pulsed stimulus of 0·1 ms duration and 25–150 V was given every second to the pudendal nerve at the level of the ischial spine by an intrarectal stimulating electrode connected to a NS6 Nerve Stimulator mounted in a Medelec MS6 Electromyography machine. The stimulating electrode was moved until a minimum conduction time with maximum amplitude of response was obtained. The stimulus to response time was measured when a supra-maximal stimulus was given. The response of the external anal sphincter was recorded by surface electrodes on the finger stall of the stimulating electrode. The stimulus to response time was recorded beneath a timebase positioned for accurate measurement.

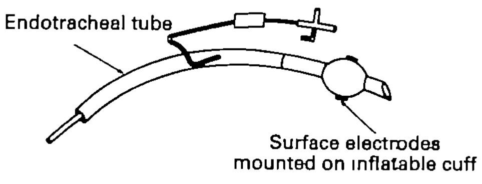

Fig. 1. Diagram of the pubococcygeus electrode.

Statistics

In the statistical analysis, Student's t-test was used unless otherwise stated. When the variance ratio between the groups was too large for Student's t-test to be valid, the non-parametric Mann–Whitney U-test (MW) was used.

Results

The results are summarized in Table 1. It can be seen that there is no significant difference in conduction time to either the external anal sphincter (P=0·50), the striated urethral sphincter (P=0·58) or pubococcygeus muscle (P=0·25) between nulliparous and parous women with normal urinary control and no prolapse.

In the following comparisons, which illustrate the important points, the women with symptoms (who are all parous) are compared with the parous women with no symptoms.

Conduction time to external anal sphincter

All the women studied had normal control of faeces. Women with stress incontinence of urine (P=0·00007), genitourinary prolapse (P=0·00004 MW) or both (P=0·0002) had a significantly prolonged nerve conduction time to the external anal sphincter compared with women with normal urinary control; this is

Table 1. Pudendal nerve conduction times and urethral closure forces in the study groups

Group	Conduction time (ms)			Maximum urethral closure pressure (cm H_2O)
	To external anal sphincter	To striated urethral sphincter	To pubococcygeus muscle	
Normal urinary control				
Nulliparous	1·6 (0·2) (n=28)	2·1 (0·3) (n=26)	1·9 (0·2) (n=17)	85 (22) (n=17)
Parous	1·7 (0·2) (n=14)	2·1 (0·2) (n=14)	1·9 (0·2) (n=9)	69 (22) (n=14)
Stress incontinence				
Alone	1·9 (0·2) (n=33)	2·8 (0·4) (n=34)	2·1 (0·3) (n=21)	41 (14) (n=33)
With prolapse	1·9 (0·3) (n=42)	3·0 (0·5) (n=42)	2·5 (0·5) (n=31)	43 (16) (n=42)
Prolapse with normal urinary control	2·1 (0·3) (n=11)	2·2 (0·2) (n=11)	2·8 (0·7) (n=8)	67 (22) (n=11)

Results are means (SD)
n, Number of patients

indicative of subclinical partial denervation of the sphincter.

Conduction time to striated urethral sphincter

Women with stress incontinence of urine, with or without genitourinary prolapse, had a significantly prolonged nerve conduction time to the striated urethral sphincter compared with women with normal urinary control ($P<0{\cdot}00001$ MW; in both cases). Of the women with stress incontinence of urine (with or without prolapse) 95% had a mean conduction time (sum of the right and left sides divided by 2) to the urethral sphincter of greater than 2·4 ms. In contrast, 4% of women with normal urinary control (with or without prolapse) had a mean conduction time greater than 2·4 ms. If the pudendal nerve conduction time is greater than 2·4 ms there is a 97% chance that the patient will have stress incontinence (see Fig. 2). Table 1 shows that the nerve conduction time to the urethral sphincter correlates with the maximum urethral closure pressure (measured with a Gaeltec catheter-tip transducer orientated anteriorly) in the different groups ($P=0{\cdot}023$ linear regression). There was no significant difference in conduction times to the striated urethral sphincter between women without prolapse and normal urinary control and those with prolapse and normal urinary control ($P=0{\cdot}086$).

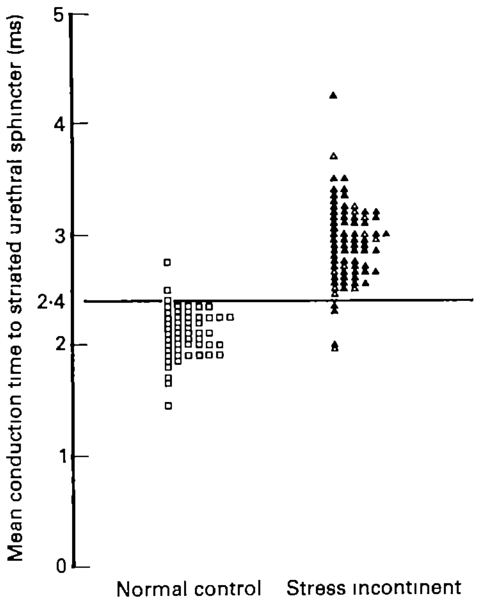

Fig. 2. Conduction time from pudendal nerve stimulation at the ischial spine to the striated urethral sphincter in normal and stress incontinent women

Conduction time to pubococcygeus muscle

Women with stress incontinence of urine ($P=0{\cdot}0022$) or genitourinary prolapse ($P<0{\cdot}002$ MW) or both ($P=0{\cdot}00001$ MW) had a significantly prolonged conduction time to the pubococcygeus muscle compared with the control women.

Discussion

The histochemical study (Gilpin *et al.* 1989) and the single-fibre electromyography study (Smith *et al.* 1989) established that women with stress incontinence of urine, with or without genito-urinary prolapse, have a significant partial denervation of the pelvic floor. The prolonged conduction time in the innervation of the external striated urethral sphincter in women with stress incontinence (with or without prolapse) indicates that the urethral sphincter weakness in these women is associated with partial denervation of the striated urethral sphincter. Women with prolapse and normal control of urine had a normal conduction time to the striated urethral sphincter (and normal maximum urethral closure pressure) showing that its innervation has been spared from injury. The differential injury to the branches of the pudendal nerve suggests that the site of denervation injury is distal and may occur within the muscle or at the neuromuscular junction. Single-fibre electromyography studies (Smith *et al.* 1989; Anderson 1984) have demonstrated that women with stress incontinence of urine have a partially denervated pelvic floor and external anal sphincter. In our study, delayed conduction in the innervation of the pelvic floor and external anal sphincter in women with stress incontinence correlates well with the electromyography.

The measurement of the pudendal nerve conduction time to the external striated urethral sphincter differentiated between women with stress incontinence and those with normal urinary control. A woman with a pudendal nerve conduction time to the urethral sphincter of greater than 2·4 ms has a 97% chance of experiencing urinary incontinence with stress.

This study shows that women with stress incontinence almost invariably have partial denervation of both the striated urethral sphincter and the pelvic floor. We infer that stress incontinence is due to a combination of factors: partial denervation of the striated urethral muscle weakening the closure forces generated by the urethra and partial denervation of the pelvic floor causing muscle weakness. This weakness may be the cause of the poor transmission of abdominal pressure changes which has been found in women with stress incontinence (Beck & Maughan 1964).

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Serum from pregnant women carrying a fetus with neural tube defect is teratogenic for rat embryos in culture

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Summary. Sera from 13 pregnant women carrying a fetus with a neural tube defect, and from 13 control women with normal pregnancies at the same stage of gestation were used in the culture of postimplantation rat embryos. Serum from women with normal pregnancies had no adverse effect on rat embryo growth and development. Serum from 10 of the women with affected fetuses had a deleterious effect on the rat embryos as abnormalities of neural tube closure were observed in 28% of the conceptuses compared to only 1·3% of the embryos cultured in control serum.

Despite extensive clinical and epidemiological research, the precise causes and mechanisms of neural tube defects (NTD) remain poorly understood. Isolated cases are believed to be multifactorial in origin (Carter 1974), involving a genetic (polygenic) predisposition and the possible interaction of numerous environmental factors which together result in abnormal morphogenesis of the nervous system.

Smithells *et al.* (1980, 1981) produced evidence that recurrence of NTD can largely be prevented by administration of multivitamins (Pregnavite forte F) around the time of conception. Moreover, in a double-blind randomized controlled trial of folic acid supplementation before conception, Laurence *et al.* (1981) found that the treated patients had no recurrence of infants with neural tube defects. From these studies it has been inferred that poor nutrition might be implicated in the causation of NTD.

To identify potential teratogens, investigators have turned their attention to animal models. Although in-vivo studies—using laboratory animals—provide the basis of most investigations into the embryopathic potential of environmental factors, experience has shown that such studies can be misleading because the mode of teratogenic action in laboratory animals is complicated by the metabolic and pharmacokinetic factors associated with the maternal system. Attempts have therefore been made to simplify experimental models to investigate whether by elimination of maternal factors, mammalian embryos themselves, during organogenesis, show intrinsic differences in susceptibility to teratogens.

Using the in-vitro rodent embryo culture technique of New (1978), it has been shown that the growth and development of postimplantation rat conceptuses from the presomite to the 25 somite stage in heat inactivated homologous serum is almost comparable to that *in vivo.* This method of maintaining embryos in culture enables the teratologist to investigate embryonic growth-supporting capacity of serum obtained from animals exposed to various environments. Soluble

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compounds can be added to the culture medium and their effects on embryos can be directly assessed.

The investigative procedures discussed above can also be applied if rat conceptuses are cultured in human serum. Reti *et al.* (1982) reported that growth and development of rat conceptuses grown in a culture medium made up of 90% human and 10% rat serum was comparable to that achieved in whole rat serum. Furthermore, it has been shown that reproducible, essentially normal, rat embryonic development is also possible in human serum supplemented with glucose and 2% rat serum. Using these modified techniques it has been observed that serum obtained from women during various stages of their menstrual cycles, pregnancy and the postpartum period supported rat embryonic development equally well (Anwar & Beck 1988).

Since serum-related embryopathic factors might be implicated in the genesis of congenital malformations it was considered to be of interest to culture and observe the response of rat conceptuses in sera from pregnant women whose fetuses were diagnosed as having a neural tube defect.

Materials and methods

Serum preparation

As soon as an NTD-affected fetus was discovered either antenatally by an ultrasound scan or at the time of delivery, the woman was asked to take part in the research project. Blood samples were obtained from 11 women before the termination of their pregnancies between 14 and 32 weeks and blood was taken from two further patients after delivery at term (Table 1).

Since the congenital anomalies were diagnosed at various gestational stages, control blood samples were obtained from volunteer women individually matched for age and stage of pregnancy. Up to 30 ml of blood was obtained from each woman; the blood samples were immediately centrifuged for 5 min at 3000 r/min at room temperature and sera treated according to the method of New (1978).

The human serum used for culture throughout was supplemented with glucose to a final concentration of 16·5 mmol/l as suggested by Chatot *et al.* (1980) and 2% rat serum (Anwar 1986): 0·2 ml of antibiotics (stock solution of streptomycin 5000 µg/ml and penicillin 5000 i.u./ml) were added per ml of culture media.

Explantation of rat conceptuses

Embryos were obtained from Wistar rats at 9·5 days gestation (timed from midnight preceding the morning on which vaginal plugs were observed), and dissected from the uterus in Hanks' balanced salt solution. Explanted conceptuses were carefully examined and only those at the late head-fold stage of development were

Table 1. Characteristics of 13 women with NTD pregnancies

	Patient no	Age (years)	Gestation at sampling (weeks)	Fetal abnormality
Group A				
	1	24	18	Spina bifida
	2	22	14	Anencephaly/spina bifida
	3	31	15	Anencephaly
	4	27	17	Anencephaly/spina bifida
Group B				
	5	35	14	Anencephaly
	6	26	32	Spina bifida
	7	29	17	Anencephaly
	8	18	PP	Hydrocephalus/spina bifida
	9	23	28	Spina bifida
	10	29	18	Spina bifida
Group C				
	11	30	20	Encephalocoele
	12	34	16	Anencephaly/spina bifida
	13	37	PP	Spina bifida

PP, Postpartum

selected for the culture experiments. It was found necessary to select the embryos carefully since Clode *et al.* (1987) have reported that early head-fold stage conceptuses are more susceptible to certain environmental changes than their slightly older litter-mates. For the purpose of the current study it was decided to use the late head-fold stage conceptuses.

Embryo culture

Conceptuses from each litter were randomly divided into experimental and control groups. Embryos were cultured at 37°C for 48 h using the roller culture method described by New (1978). On average each bottle contained five conceptuses in 5 ml of culture medium. The number of conceptuses used in an experiment varied with the size of a litter on a particular day; 36 litters were used to complete the experiments. From previous experimental data using a cumulative means frequency analysis it was calculated that about 10 embryos were necessary to be cultured in a serum sample to obtain statistically valid results.

Serum from each patient was divided into two portions. Experiments were performed on two separate occasions using serum from each patient and her matched control to ensure consistency.

Assessment of embryonic growth and development

At the end of the culture period, the yolk-sac diameter and crown–rump lengths of embryos were measured. Embryonic development and differentiation was assessed by examining 14 different morphological features on a points scoring system developed by Brown & Fabro (1981), which enables the identification of growth retardation and developmental anomalies. Further growth assessment was made by estimating the total protein content in each embryo by the method of Lowry *et al.* (1951). Statistical significance of the results was analysed using the paired *t*-test.

Results

For statistical analysis patients and controls were considered as two separate homogeneous populations, hence results were pooled into two groups. These show that serum from patients with NTD pregnancies supported embryonic growth less well than serum from women whose pregnancies were unaffected (Table 2).

Detailed examination of the results obtained suggested that the women with NTD-affected pregnancies could be categorized into three subgroups defined by the capacity of the serum to

Table 2. Proportion of rat embryos developing abnormally in culture with serum from pregnancies affected by neural tube defects (NTD) compared with age-matched control pregnancy serum

	NTD-affected pregnancy serum		Control pregnancy serum	
Patient no.	No. of embryos cultured	No. of abnormal embryos	No. of embryos cultured	No. of abnormal embryos
Group A				
1	10	10	10	1
2	11	11	12	0
3	10	8	10	0
4	11	10	10	0
Group B				
5	15	1	14	1
6	16	4	15	0
7	15	1	14	0
8	15	0	15	0
9	12	0	15	0
10	12	0	12	0
Group C				
11	11	0	10	0
12	11	0	10	0
13	10	0	10	0
Total	159	45	157	2

support rat embryonic growth in the culture medium.

Serum samples from four patients, designated as group A, were found to be highly embryopathic. Six patients, designated as group B, had moderately embryopathic sera and serum samples from the remaining three women, designated as group C, had no adverse effects on embryonic growth and development (Table 3).

Morphological scores, yolk sac diameter, crown–rump length, somite number and protein values were significantly reduced ($P<0·01$) in conceptuses cultured in serum from patients in group A when compared with their controls (Table 3).

Of the 42 rat embryos cultured with sera from the four NTD pregnancies in group A, 93% developed abnormally and over 72% of these were found to have open neural tubes in the region of fore, mid or hind brain. A significantly higher proportion of the remaining experimental embryos in this group were anophthalmic or had otic vesicle and trunk anomalies compared with their respective controls.

Although the number of developmental abnormalities in experimental embryos grown in sera from the NTD pregnancies in group B were considerably fewer than in group A (Table 3), indices of embryonic growth including morphological scores, yolk sac diameter, crown–rump length, somite number and protein values were significantly reduced in conceptuses grown with sera from these patients compared with controls (Table 3).

Embryonic growth and development in sera from women in group C was comparable to that in controls (Table 3).

Discussion

Our experiments demonstrate that supplemented serum from a substantial proportion (10 of 13) of women with NTD-affected pregnancies is less efficient in supporting rat embryonic growth than serum from women with normal pregnancies whose serum always supported normal growth. These findings imply that serum-related environmental factors might be causally associated with neural tube defects.

Since the differentiation and formation of the human neural tube takes place within the first trimester, prospective studies should ideally be performed during this stage of pregnancy. It is possible that transitory adverse changes in serum could cause NTD and, thus, embryo culture experiments would need to be performed at regular intervals throughout the first trimester in order to detect temporary fluctuations in the capacity of human serum to support embryonic growth. Nevertheless, even though blood samples were obtained at various stages of gestation (Table 1), serum from 4 of 13 of the women (group A) was grossly inadequate in supporting rat embryos. From the small study reported here it seems possible that embryopathic factors in

Table 3. Growth indices of rat embryos cultured in sera from patients with NTD-affected pregnancies compared with age-matched control sera

	Group A		Group B		Group C	
Growth index	Patients	Control	Patients	Control	Patients	Control
No of embryos	42	42	85	85	32	30
Morphological score	30·63***	42·41	41·31***	42·17	42·94***	42·04
	(1·40)	(0·07)	(0·28)	(0·09)	(0·03)	(0·44)
Yolk sac diameter (mm)	3·76***	3·91	3·99***	4·10	3·73***	3·97
	(0·05)	(0·03)	(0·03)	(0·03)	(0·04)	(0·03)
Crown–rump length (mm)	2·63***	2·91	3·05***	3·24	2·95	3·00
	(0·08)	(0·04)	(0·02)	(0·03)	(0·05)	(0·05)
Somite number	21·35***	25·73	25·22***	25·67	26·67	26·48
	(0·68)	(0·23)	(0·12)	(0·16)	(0·08)	(0·16)
Embryonic protein (μg)	130·64***	157·92	134·06	163·44	176·69	176·86
	(2·35)	(4·92)	(6·82)	(3·01)	(3·36)	(5·76)
Per cent abnormal embryos	92·9*	2·4	7·1	1·2	0	0

Results are mean (SE) values.

Significance of difference between patients and control*** $P<0·01$ (paired t-test), * $P<0·001$ (χ^2-test).

the human serum might be present throughout pregnancy.

Most of the developmental anomalies observed in the cultured embryos were found to be those affecting the central nervous system. This is due to the fact that the formation and closure of the neural tube in the rat is completed during the period covered by the whole embryo culture system. As a result there is increased sensitivity of the CNS to embryopathic effects and our findings do not necessarily imply a system specificity for the putative teratogen involved. Furthermore, results from the current study must be viewed in context, bearing in mind that the in-vitro embryo culture model is a closed system and does not reproduce the dynamic in-vivo feto-maternal situation.

Results from this small study are encouraging since the culture model suggests the possibility that certain women may have identifiably embryopathic sera. It would be of interest to measure various vitamins and essential trace elements in the blood of women whose sera consistently give suboptimal rat embryonic growth.

Further experimental work involving embryo cultures using sera from high-risk patients is needed. If our findings are confirmed on a large scale these types of studies might have a place as part of a prepregnancy screening programme.

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The fetal outcome in a randomized double-blind controlled trial of labetalol versus placebo in pregnancy-induced hypertension

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Summary. The effects of labetalol were compared with those of placebo in a multicentre randomized double-blind and prospective study of 152 patients with mild to moderate, non-proteinuric pregnancy-induced hypertension. Labetalol in a dose of 100 mg three times daily, increasing to 200 mg three times daily where required, significantly reduced maternal mean arterial pressure. There was some reduction in preterm delivery, neonatal respiratory distress syndrome and jaundice in the labetalol-treated group. Intrauterine growth retardation and neonatal hypoglycaemia occurred with the same frequency in both groups. There were no perinatal deaths. Labetalol appears to be an effective agent in the management of mild to moderate pregnancy-induced hypertension. The data from this study suggest possible advantages and no apparent disadvantages for the fetus during its use.

Antihypertensive therapy is an essential part of the management of acute and severe pregnancy-induced hypertension (PIH). The value of antihypertensive therapy in mild hypertensive disease in pregnancy is much less certain. Non-proteinuric PIH has been said to have little or no effect on birthweight and perinatal outcome (MacGillivray 1977, 1982; Long *et al.* 1980), though a more recent controlled study suggests that a mild deleterious effect does exist (Ounsted *et al.* 1985). As the disease process progresses, so birthweight is reduced and perinatal morbidity and mortality increase (MacGillivray 1983; Clinch 1980; Symonds 1980). In order to be of value, therefore, not only should hypotensive agents be able to lower maternal blood pressure, reduce hospital admissions and, ideally, prevent the onset of proteinuria, but they must themselves also have no adverse effects on fetal outcome, and should be advantageous in reducing neonatal morbidity.

Many studies have been undertaken to examine the effect of antihypertensive therapy in proteinuric PIH, essential hypertension and in combination with mild to moderate hypertension (Redman *et al.* 1976; Lieberman *et al.* 1978; Gallery *et al.* 1979; Lamming *et al.* 1980; Michael & Potter 1981; Leather *et al.* 1968). However, determination of the value of antihypertensive therapy in non-proteinuric, mild to moderate PIH has been confined to one randomized double-blind study (Rubin *et al.* 1983). This study concluded that there were no adverse fetal effects from the use of the beta-blocker atenolol, although neonatal bradycardia was a transient problem in some cases.

Labetalol, a combined alpha- and beta-blocker has been used in the treatment of proteinuric PIH and has been shown to be at least as effective as methyldopa in lowering blood pres-

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sure when compared directly (Lamming *et al.* 1980; Redman 1981), whilst no disadvantages to fetal outcome were noted by either trial. Furthermore, it has not been shown to have any significant adverse neonatal effects (Macpherson *et al.* 1986) in the term infant. Babies born to mothers taking labetalol showed a transient reduction of systolic blood pressure when compared with babies from mothers not treated, though no adverse effect was noted on other indices of sympathetic function. This contrasts with babies born to mothers treated with methyldopa who had statistically significant hypotension during at least the first 3 days after birth (Whitelaw 1981). No placebo-controlled trial of the use of labetalol in mild to moderate PIH has yet been undertaken. This present study was, therefore, undertaken to study the effects of early intervention therapy with labetalol or placebo on pregnancy outcome with particular emphasis on certain aspects of fetal well-being which might be affected by maternal treatment with beta-blockers or labetalol. One benefit of such treatment is suggested by an increase in phospholipid concentration found in the fetal lung by Nicholas *et al.* (1978) after labetalol administration in rabbits together with a somewhat lower frequency of respiratory distress syndrome. On the other hand, there exists the possibility of an increase in the rate of spontaneous preterm delivery since the beta-blocking effect of labetalol could theoretically increase myometrial contractility with subsequent effects on birthweight and growth retardation. This report describes the fetal outcome of the study with especial reference to these points. Detailed analysis of the maternal course will be presented elsewhere.

Patients and methods

The occurrence of fetal growth retardation may be defined either with reference to the appropriate normal distribution of weight-for-gestational-age corrected for sex, or by the imposition of an arbitrary cut-off point of, say, 2500 g. If the 10th centile were taken as the lower limit of 'normality', then 67 mothers would need to be recruited into each arm of the trial to allow detection of a doubling of this rate ($\gamma=0{\cdot}05$; $\beta=0{\cdot}5$). In fact, 152 patients were entered into the trial from the five centres (Queen's Medical Centre, Nottingham; Kings Mill Hospital, Mansfield; The City Hospital, Nottingham; The City Hospital, Derby; North Staffordshire Hospital Centre, Stoke on Trent) during the 18 months of the study. Criteria for entry were a blood pressure of 140–160 mmHg systolic and 90–105 mmHg diastolic after 15 min rest on two occasions separated by 24 h, between 20 and 38 weeks gestation, and an absence of proteinuria. Women were excluded if they gave a past history of hypertension which antedated pregnancy, or had a history of metabolic, renal, cardiovascular, respiratory or collagen disease. Once entered into the trial, all decisions regarding further management, including hospital admission, were taken by the patient's own obstetrician.

All patients except five from an outlying hospital were initially admitted for a minimum period of 24 h rest and assessment. The patients were then allocated in a double-blind and randomized manner to treatment. Labetalol and identical placebo tablets were supplied by Duncan Flockhart directly to the pharmacies of the participating hospitals, together with a list of random numbers. The individual pharmacies then issued active or placebo tablets to each patient as she was recruited. Thus neither the physicians in charge nor the patients themselves were aware of the treatment being administered. Patients were instructed to take one tablet three times daily; this dose was increased to a maximum of two tablets three times daily if in the judgment of the obstetrician the blood pressure was not controlled. If there was no improvement at the maximum incremental dose, consultants initiated antihypertensive therapy with a drug or drugs other than labetalol. Recordings of blood pressure, using ordinary mercury sphygmomanometers, were taken at weekly intervals from entry to the trial until delivery. The patients rested in the semirecumbent position for at least 5 min before measurement of blood pressure. Diastolic blood pressure readings were taken at the phase IV Korotkoff sounds. Mean arterial pressure (MAP) for the two groups was calculated as the diastolic pressure plus one-third of the difference between systolic and diastolic pressures. The blood pressure recordings are expressed in weeks since entry to the trial rather than at gestational age to allow direct comparison of the data.

The gestational age at delivery, birthweight, sex, Apgar score and 5-min heart rates were recorded, as well as the need for admission to, and time spent in, the special care baby unit

(SCBU). The development of respiratory distress syndrome requiring ventilation, or jaundice (serum bilirubin >250 μmol/l) was recorded. Heel-prick blood samples for measurement of blood glucose concentration were taken from all infants admitted to the SCBU, and from any others where there were clinical indications. Hypoglycaemia (blood glucose <1·4 nmol/l) was recorded. Intrauterine growth retardation (IUGR), defined as a birthweight <10th centile for sex and gestational age, and severe IUGR, defined as a birthweight <5th centile for sex and gestational age, were also recorded. Statistical analysis was undertaken using the SPSS-X statistical package (SPSS-X User's Guide 1983) on an ICL 2976 computer. Results are expressed as means (SD). The blood pressure data were sequentially analysed and compared using the Mann–Whitney *U*-test. Other normally distributed continuous variables were compared by two-tailed unpaired *t*-tests. Discontinuous variables were compared by means of cross-tabulation, χ^2 and Fisher's exact tests.

The study protocol was scrutinized and approved by the ethics committees of the participating hospitals. The participants gave informed verbal consent for the study.

Results

Overall 152 women were entered into the trial from the five centres. Eight were excluded for the following reasons. Two women withdrew themselves; two others did not follow the protocol, one of whom was treated with ward stock labetalol by mistake instead of being entered through the randomization procedure and the other developed a rash and was found to be on labetalol when the code was broken. The other four did not fulfil the stipulated admission criteria: one fulminated before entry; one had essential hypertension; one had a diastolic blood pressure >110 mmHg at entry; and the fourth had proteinuria at entry. Thus, 144 patients were included in the analysis, of whom 70 were treated with labetalol and 74 with placebo. The patients' characteristics are outlined in Table 1. There were no significant differences between the groups on the basis of age, number of cigarette smokers, parity or past history of PIH.

The mean arterial pressure dropped equally in both groups with bed-rest alone (day 1) from 111·0 (SD 4·8) to 108·7 (SD 6·3) mmHg in the labetalol group and from 110·6 (SD 13·2) to 106·0 (SD 12·3) mmHg in the placebo group. However, when treatment was started there was a further and significantly greater fall in mean arterial pressure in the labetalol group (mean 108·0, SD 6·3 to mean 99·8, SD 8·6 mmHg) ($P<0·001$) compared with the small and non-significant fall seen in the placebo group (mean 106·7, SD 12·3 to mean 105·5, SD 10·7 mmHg). Furthermore, this fall in mean arterial pressure in the labetalol group was sustained over a 5-week period ($P<0·01$) so that at week 5 the mean arterial pressure in the labetalol group was mean 100·20 (SD 19·7) mmHg compared with 109·2 (SD 10·6) mmHg in the placebo group ($P<0·05$).

The outcome for all the infants is shown in Table 2. It can be seen that there was an excess of severely growth-retarded babies (<5th centile) in the labetalol group. However, five of these babies were assessed as being severely growth retarded before entry into the trial as judged by

Table 1. Clinical characteristics of the women in the two treatment groups

	Labetalol (*n*=70)	Placebo (*n*=74)
Age (years)	27·5 (5·8)	24·7 (4·8)
Smokers	11 (16%)	9 (12%)
Primigravidae	46 (66%)	57 (77%)
Past history of PIH	16 (23%)	8 (11%)
Past history of perinatal death	1 (1%)	1(1%)
Fetus judged to be severely growth retarded at entry	5	0
Mean arterial pressure at entry (mmHg)	111·0 (4·8)	110·6 (13·2)
Gestational age at onset (weeks)	34·0 (2·7)	34·2 (2·6)
Gestational age at delivery (weeks)	37·8 (2·2)	37·5 (1·9)

Results are means (SD) and *n* (%) as appropriate.
There were no significant differences between the two groups using the *t*- and χ^2-tests as appropriate.

Table 2. Fetal outcome in the two treatment groups

	Labetalol (n=70)	Placebo (n=74)	Relative risk ratio*	95% CI on risk ratio
Perinatal deaths	0	0		
Birthweight (g) mean (SD)	2948 (756)	2913 (569)		
Number of babies <10th centile	10 (14%)	5 (7%)	2·3	-0·7 to 7·1
Number of babies <5th centile at start of trial	5	0		
Number of babies <5th centile at end of trial	6 (9%)	1 (1%)		
Preterm delivery (<37 weeks)	12 (17%)	17 (23%)	0·7	0·3 to 1·6
Transferred to SCBU	10 (15%)	9 (12%)	1·2	0·5 to 3·2
Developed respiratory distress syndrome (RDS)	1	3		
No. of babies delivered electively preterm	11	14	0·8	0·3 to 1·9
No with RDS after elective delivery	1	3		
Developed jaundice	5	10	0·5	0·2 to 1·5
Developed hypoglycaemia	4	3		
Time spent in SCBU (days) median	0	0		
(range)	(0–53)	(0–58)		
No. with bradycardia (<120 beats/min)	4	4		

*Relative risk ratios were calculated where there were five or more observations. There were no statistically significant differences between the two groups using *t*-test, χ^2- and Fisher's exact test where appropriate.

both clinical assessment and ultrasound scanning of biparietal diameter and abdominal circumference. Furthermore, tests of placental function, using serum oestriol with or without human placental lactogen (hPL), in these women at entry into the trial showed values which were more than 2 SD below the mean, whereas no babies were severely growth retarded in the placebo group using the same criteria at entry to the trial.

In view of this disparity in the initial data, a further analysis of fetal outcome was performed after these babies were excluded. The gestational ages at onset of PIH were similar (labetalol 34·0 weeks, SD 2·7 *vs* placebo 34·2 weeks, SD 2·6) as were the gestational ages at delivery (labetalol 38·0 weeks, SD 2·1 *vs* placebo 37·5 weeks, SD 1·9), the number of patients induced (labetalol 53% *vs* placebo 57%) and the number of elective caesarean sections (20% in each group). There were no perinatal deaths or congenital malformations in either group. Mean birthweights were similar in the two groups (labetalol 3066 g, SD 644 *vs* placebo 2913 g, SD 569), and the number of small babies (<5th centile) was the same in the two groups. However, a trend was apparent in that the babies in the placebo group were more often preterm (17 *vs* 8 in labetalol group) and more often transferred to the special care baby unit (9 *vs* 4) and were more likely to develop neonatal respiratory distress syndrome (3 *vs* 0) or jaundice (10 *vs* 4) although none of these differences was statistically significant (Fisher's exact test). Bradycardia at 5 min and hypoglycaemia occurred with the same frequency in both groups (Table 2). The median number of days spent in the special care baby unit was similar in the two groups (labetalol 0, range 0–53 *vs* placebo 0, range 0–58).

The number and proportions admitted to the trial before 31 weeks, between 31 and 36 weeks and after 36 weeks are outlined in Table 3. It should be noted that in both groups the gestational age at onset of treatment had a wide spread from 25 to 37 weeks. Furthermore, it is well known that early onset PIH is more likely to result in the development of proteinuria and markedly raised blood pressure and that this is associated with a poorer fetal outcome. In view of this, both groups were analysed separately to determine whether there was any disparity in the results between early onset (before 31 weeks)

Table 3. Distribution by gestational age at admission to the study in the two treatment groups

Gestation at admission (weeks)	Labetalol (n=70) n (%)	Placebo (n=74) n (%)
<31	10 (14)	10 (14)
31–36	54 (77)	54 (73)
>36	6 (9)	10 (14)

and late onset (after 36 weeks). This separate analysis showed no statistically significant differences between the groups at either range of gestational age at onset for: days of treatment, gestational age at delivery, birthweight or the prevalence of small infants. However, 7 of the 10 patients who developed PIH early in the placebo group were judged to require additional antihypertensive therapy, compared with only one of the 10 early onset patients in the labetalol group, whilst none of the patients in either group required additional therapy when PIH developed after 36 weeks.

Discussion

In comparison with placebo, labetalol reduces the mean arterial pressure in patients with PIH. It is important that this reduction in blood pressure does not lead to a deterioration in outcome for the fetus. Furthermore, labetalol should not adversely affect the fetus after delivery. Macpherson *et al.* (1986) have shown that babies born at term to women taking labetalol experience no adverse effects other than mild reduction of blood pressure in the first 24 h after delivery. In particular, no significant change in heart rate was noted. This study was carefully case-controlled and all measurements of blood pressure and heart rate were made by a single observer. Even so, the hypotensive effect observed was small. We thus felt that in a multicentre trial there was nothing to be gained by an attempt to measure the blood pressure and heart rate of all newborn infants beyond the 5-min Apgar score.

Many studies of antihypertensive agents in pregnancy have shown some improvement in outcome for the fetus or at worst no apparent adverse effects. Methyldopa appeared to confer a small improvement in birthweight and duration of gestation in a 'late-entry' group (Redman *et al.* 1976) by comparison with controls. The non-selective beta-blocker oxprenolol seemed to reduce intrauterine growth retardation still further when compared with methyldopa (Gallery *et al.* 1979). However, this effect was not observed when the cardioselective beta-blocker atenolol was tested against placebo (Rubin *et al.* 1983), although there was a reduction in respiratory distress syndrome. This has also been claimed for labetalol when compared with methyldopa (Redman *et al.* 1976) or other antihypertensive agents (Michael & Potter 1981). The beta-blocker propranolol apparently increased the frequency of fetal growth retardation (Lieberman *et al.* 1978), but this was a poorly controlled study with an excess of women with renal disease in the treatment group. The quality of previous published studies varies, some were not concerned solely with PIH, others did not compare active treatment with placebo, or were not double-blind, or considered small numbers of patients. We concede that although our study comprised more women than any other study, it still falls short of the definitive numbers of patients required to make bold statements about labetalol alone, but we believe that it adds to the body of knowledge on beta-blockade in PIH.

By chance, in the present study, the only babies that were severely growth retarded before the onset of treatment were allocated to the labetalol group. Labetalol did not improve growth in these growth-retarded babies and labour was induced in all five pregnancies for fetal growth retardation. However, all of these babies were born in good condition and had a good neonatal outcome. In fetuses with normal growth patterns at entry to the trial, labetalol conferred neither advantage nor disadvantage in terms of birthweight or growth retardation. This is in agreement with evidence from previous trials (Rubin *et al.* 1983; Redman 1981).

In theory beta-blockade could cause preterm labour. However, as shown in other studies (Redman 1981; Gallery *et al.* 1979; Michael & Potter 1981), this does not occur. In this study, spontaneous preterm labour (<37 completed weeks gestation) occurred, if anything, less often in the labetalol group (one woman) than in the placebo group (three women).

The present randomized double-blind controlled trial indicates that labetalol is able effectively to lower mean arterial pressure in women with PIH. This reduction allowed the safe continuation of pregnancy without adversely affecting the fetus, presumably because the better control of maternal blood pressure reduced the perceived need for early delivery. However, the fact that no antihypertensive therapy was judged to be necessary in either the placebo- or the labetalol-treated groups where the PIH was of late onset suggests that antihypertensive therapy is unnecessary for mild or moderate disease at this stage of pregnancy. However, there can be differences between statistical and biological indices of neonatal well-being. A reduction in the number of preterm deliveries and the fewer babies with jaundice and respiratory distress syndrome associated with maternal labetalol therapy do suggest a biological improvement for preterm deliveries. Within the limits outlined previously, labetalol is a safe antihypertensive agent in women with mild or moderate PIH in the early third trimester.

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The use of ultrasound examinations, intrapartum fetal heart rate monitoring and beta-mimetic drugs in France

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Summary. We conducted a survey of French obstetricians to document their attitudes towards routine ultrasound, intrapartum fetal monitoring and beta-mimetics in 1987. A questionnaire was sent to 582 obstetricians or gynaecologists who were members of two French medical associations. The response rate was 85%. Of the respondents 92% prescribed two or three routine ultrasound examinations; only one doctor did not use electronic fetal monitoring and 99% of the respondents prescribed beta-mimetics to prevent preterm delivery. Some obstetricians reported a decrease in their use of ultrasound and more dramatically in the use of beta-mimetics. Side-effects were reported to be the major reason for the change in beta-mimetic use. Obstetricians who read English language journals were more likely to have reduced their use of ultrasound and beta-mimetics than those who read only French language journals.

Over the last 20 years, obstetric care has been marked by an increasing use of screening tests, treatments, antenatal visits and hospitalization. But recently concern has been expressed about benefits and side-effects of such care. Wide differences in practice have been observed between countries which have similar pregnancy outcomes (Blondel *et al.* 1985; Kaminski *et al.* 1988) and there is little evidence in the literature about the extent to which these variations in care lead to differences in maternal and infant health (Enkin & Chalmers 1982; Kaminski *et al.* 1986).

Ultrasound examinations, intrapartum fetal monitoring and beta-mimetics are interesting examples of this debate. The six randomized controlled trials of routine ultrasound reported so far have come to apparently contradictory conclusions concerning the recommendation of this screening procedure for all pregnant women (Thacker 1985; Grant 1986; Ringa *et al.* 1987). Pooling data from these trials also failed to demonstrate any beneficial effect (Thacker 1985). This uncertainty has been expressed by differences in the conclusions of the Royal College of Obstetricians and Gynaecologists' Working Party (RCOG 1984) and the three consensus conferences that have been held in other countries: in the USA it was recommended that ultrasound examination should be performed only for specific indications (NIH 1984); one routine ultrasound examination was recommended in Norway (Backe & Rudinow Soetman 1986) and in the UK (RCOG 1984) and two routine examinations were recommended in France (Tournaire *et al.* 1987). Six randomized controlled trials comparing electronic fetal monitoring (EFM) with intermittent auscultation during labour found no differences in Apgar scores and mortality rates independently or after pooling data from each trial (Thacker 1987). The trial in Dublin found a decrease in the frequency of neonatal seizures in the EFM group, but three infants with seizures at birth had neurological sequelae at 1 year of age in the monitored group and three also in the control group of women (MacDonald *et al.* 1985). Furthermore, the review of these randomized control trials

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(RCTs) demonstrated a significant increase in the rate of caesarean section with a policy of routine EFM (Thacker 1987). None of the RCTs which compared beta-mimetic administration with placebo showed any benefit in reducing perinatal mortality, and a pooled analysis of these trials showed that although beta-mimetic drugs delay delivery for at least 24 h and reduce the proportion of delivery before 37 weeks gestation, no significant difference was observed for perinatal mortality and neonatal respiratory disorders (King *et al.* 1985). Furthermore, administration of beta-mimetic drugs produces unfavourable side-effects on maternal and infant health (Thiery 1986).

It was against this background that we wanted to know how obstetricians rely on these procedures and treatments in France. Data from a national sample of births in France in 1981 showed that most women had ultrasound examinations during pregnancy and EFM during labour (Rumeau-Rouquette *et al.* 1984), and 15% of the pregnant women received beta-mimetics (Bréart & Ringa 1986). Many papers which discussed the efficacy of these three aspects of antenatal care have been published since 1981. We decided to examine the influence of these findings on current practice in France. The aims of this study are thus (i) to describe how French obstetricians use ultrasound examinations, intrapartum fetal monitoring and beta-mimetic drugs, and the trend in the use of these practices since 1980, and (ii) to document the arguments used by obstetricians and gynaecologists to support their practice.

Data and methods

A questionnaire with a reply-paid envelope was sent to all members of the Collège National des Gynécologues et Obstétriciens Français (CNGOF) and to the obstetricians who were members of the Société Française de Médecine Périnatale (SFMP). A first letter was dispatched in January 1987 and a second one was sent 2 months later to those who had not replied.

Of the 582 gynaecologists and obstetricians who received the questionnaire, 495 (85%) replied. We excluded 19 persons from the analysis because they were retired or they practised gynaecology only. The data on ultrasound and use of beta-mimetics were based on 476 gynaecologists or obstetricians who provided antenatal care and the results on intrapartum fetal monitoring were based on 455 obstetricians who attended deliveries.

The questionnaire included questions about ultrasound examination, beta-mimetic drugs and EFM. Gynaecologists and obstetricians were asked whether or not they prescribed them, and how long they had used them; they were requested to support their attitude by classifying a list of opinions according to their importance. There were also several questions about doctors' characteristics (the year they became an obstetrician or gynaecologist, the place of practice and the medical journals which they read). The relation between the practice and the characteristics of the doctors was studied using the Pearson χ^2-test.

Results

Doctors' characteristics

Of the 476 gynaecologists and obstetricians, 14% had begun to practise before 1960, 28% between 1960 and 1969, 48% between 1970 and 1979 and 10% in 1980 or later; 52% were working in the public sector only (public hospital), 19% in the private sector only (maternity unit or private surgery) and 29% in both private and public sectors. When considering the size of the maternity unit, 25% of the obstetricians were working in a unit which had fewer than 1000 deliveries per year and 29% of the obstetricians were in a unit which had more than 2000 deliveries per year. Of those who responded, 51% read at least one of the following journals: *British Journal of Obstetrics and Gynaecology, American Journal of Obstétrics and Gynecology* or *European Journal of Obstetrics and Gynecology and Reproductive Biology*; 48% of the respondents read only the following French journals: *Journal de Gynécologie Obstétrique et Biologie de la Reproduction, Revue Française de Gynécologie Obstétrique* or *Gyn-Obst.*

Routine ultrasound examination

Of the doctors who provided antenatal care 99% used routine ultrasound screening for every pregnant woman. When there was no complication, 2% of the respondents said that they prescribed only one ultrasound examination, 47% two, 45% three and 6% four or more.

For 28% of the respondents, their current policy concerning the number of routine ultrasound examinations started before 1980, for 48% between 1980 and 1984 and for 24% of them since 1985. This latter group includes 14% of respondents who increased the number of ultrasound examinations and 10% who decreased it. There was no significant relation between the number of ultrasound examinations prescribed in 1987 and the change in policy since 1985. This change was not linked to the place of practice nor to the year the respondent became an obstetrician or gynaecologist; but it varied according to the journals which were read: doctors who read journals written in English were more likely to have decreased the number of ultrasound examinations than doctors who read French journals only (13% *vs* 6%) ($P<0{\cdot}05$).

The principal indication mentioned for ultrasonography was for the identification of fetal abnormalities (Table 1). The other indications were ranked in the following order: to determine gestational age, to check fetal growth, to detect multiple pregnancies and abnormalities of the placenta; each of these indications was reported by more than 90% of the doctors who used routine ultrasound examinations.

Overall, 96% of the respondents considered that improvement in diagnosis and in pregnancy outcome were reasons for obstetric ultrasonography and the latter was classified first most frequently (Table 2); 65% of the doctors mentioned women's demand and the safety of the procedure as reasons for ultrasonography and most of the time these reasons were ranked at the third or the fourth level in the list of reasons.

Intrapartum fetal heart rate monitoring

Only one person out of 455 who attended deliveries did not use EFM during labour. This screening was mostly applied to every woman: 1% of the respondents used it for high-risk women only. This pattern of practice was established before 1975 by 39% of the obstetricians, between 1975 and 1979 by 37% and after 1980 by 24%.

Most of the obstetricians gave earlier detection of fetal distress as the first reason for their using EFM and improvement of perinatal outcome as the second reason (Table 3). The other reasons listed in the questionnaire were mentioned less often. In order of importance, they were: (i) continuous surveillance without increased number of midwives, (ii) safe examination, (iii) nobody knows any longer how to look after women in labour without EFM, and (iv) women's demand.

Beta-mimetics

Overall, 99% of the respondents said that they used beta-mimetics for the prevention of preterm delivery. When asking doctors when they prescribed these drugs, 74% of them said that they administered oral beta-mimetics prophylactically, 63% used intravenous or oral beta-mimetics when they detected signs of premature maturation of the cervix, 76% in women with ruptured membranes and 49% when the cervix was ≥4 cm dilated.

For 65% of the obstetricians the principal reason given for using beta-mimetics was the tocolytic effect of these drugs. For 38%, it was delay of delivery (Table 4). Two other reasons (better compliance with rest and their psychological effect) were less often quoted and they were mostly the third and the fourth reasons for using these drugs.

Overall 38% of the doctors had not changed their practice concerning the use of beta-mimetics since 1980, 11% had prescribed them more often and 51% less often. This decrease was not linked to their place of practice nor to the year they became a specialist. Obstetricians who read journals written in English were more likely to have reduced beta-mimetic use (54%) than obstetricians who read French journals only (46%) ($P<0{\cdot}05$).

Side-effects of the treatment were more frequently reported as reasons for decreasing beta-mimetic use (90%) than the lack of effectiveness of these drugs (74%) and the former was more frequently mentioned as the first reason (Table 5). Improvement in nenonatal care and the existence of other treatments to prevent preterm delivery were rarely given as the principal reason.

Discussion

In this survey, 15% of the members of the two associations (CNOG and SFMP) did not reply. Some of them have moved or were retired, but the main reason was that some members of the Collège were gynaecologists and did not practise obstetrics. At the beginning of the questionnaire they were asked to answer that they did not provide antenatal care nor attend deliveries and

Table 1. Indications for routine ultrasound examination according to order of importance

In your opinion, what are the main indications for prescribing ultrasound examinations? (Rank them according to order of importance)		Order of importance* †						
		1st	2nd	3rd	4th	5th	6th	All
Identification of fetal abnormalities	(%)	52·7	22·7	11·1	7·1	4·7	0·4	98·7
Determination of gestational age	(%)	43·0	23·1	15·0	10·3	6·0	0·0	97·4
Checking fetal growth	(%)	18·0	30·2	32·8	12·6	4·3	0·0	98·7
Detection of multiple pregnancies	(%)	8·8	16·1	16·7	28·7	23·3	0·6	94·2
Detection of placental abnormalities	(%)	6·0	6·1	14·1	26·6	38·8	0·6	92·7
Other indication	(%)	0·2	0·8	0·2	0·4	0·6	2·5	4·8

n = 468.

* Respondents may have attributed the same order of importance to several items.

† Items have been rearranged according to decreasing frequencies.

Table 2. Reasons for using routine ultrasound examination according to order of importance

Why do you prescribe one ultrasound examination or more to every pregnant woman? (Rank your reasons according to order of importance)		Order of importance*					
		1st	2nd	3rd	4th	5th	All
Improvement in pregnancy outcome	(%)	56·8	33·8	4·3	1·1	0·0	95·9
Improvement in diagnosis	(%)	43·4	49·4	2·3	0·6	0·0	95·7
Women's demand	(%)	1·7	6·0	28·4	29·1	0·0	65·2
Safe examination	(%)	0·8	4·1	35·0	23·9	1·1	65·0
Other reason	(%)	2·1	1·7	3·2	0·8	1·7	9·4

n = 467.

* See footnotes to Table 1.

to send back the questionnaire; some of them may not have returned it.

However, the respondents were not a representative sample of French obstetricians. To join a medical association is not compulsory in France. The CNOG and the SFMP are two out of the three French associations including obstetrics in their definition. Each of these two associations has an annual meeting and publishes a book with the main papers of this meeting. An obstetrician has to be fully qualified and to receive the support of a member of the Collège National des Gynécologues et Obstétriciens Français before joining the Collège. The obstetricians from this sample can be expected to be particularly aware of the debate on effectiveness and side-effects of procedures or drugs which can be used during pregnancy and delivery.

Nearly all the respondents prescribed routine ultrasound examinations. This policy is widespread in Europe: of 67 maternity units from every country of the European Community, 82% use this for routine screening of every pregnant woman (Heringa & Huisjes 1988). In our survey the attitude regarding the number of routine ultrasounds was close to the current French regulation and recommendations. Two examinations are reimbursed for all pregnant women and a National Insurance agreement is requested for reimbursing any examination above that number. Two or three examinations were recommended by some French obstetricians (Chartier 1982; Sureau & Uzan 1986) and

Table 3. Reasons for using intrapartum fetal heart rate monitoring (EFM) routinely according to order of importance

Why do you use EFM for every woman in labour? (Rank your reasons according to order of importance)		Order of importance*						
		1st	2nd	3rd	4th	5th	6th	All
Early detection of fetal distress	(%)	85·0	13·4	0·7	0·0	0·2	0·0	99·3
Improvement in perinatal outcome	(%)	15·9	66·0	10·7	0·7	0·0	0·2	93·7
Continuous surveillance without increased number of midwives	(%)	5·4	8·3	32·4	8·5	5·8	2·5	62·8
Safe examination	(%)	0·0	2·0	10·5	14·6	11·2	0·2	50·1
Nobody knows any longer how to look after a woman in labour without EFM	(%)	1·8	3·6	13·0	15·4	7·4	8·5	49·7
Women's demand	(%)	0·7	0·7	4·2	13·0	15·0	10·5	44·1
Other reason	(%)	0·4	0·9	1·3	0·7	0·9	0·7	5·6

n = 460.
*See footnotes to Table 1.

Table 4. Reasons for using beta-mimetics according to order of importance

Why do you prescribe beta-mimetics? (Rank your reasons according to order of importance)		Order of importance*					
		1st	2nd	3rd	4th	5th	All
To stop uterine contractions	(%)	64·6	28·8	0·9	0·4	0·0	94·8
To delay delivery	(%)	38·5	47·4	5·2	1·1	0·0	92·2
To improve compliance with rest	(%)	2·8	9·6	39·6	5·6	0·4	58·0
To have a psychological effect	(%)	0·6	2·2	10·0	37·8	0·0	50·6
Other reason	(%)	0·2	0·0	0·6	0·4	0·2	1·5

n = 460.
* See footnotes to Table 1.

Table 5. Reasons for decreasing beta-mimetic use according to order of importance

Why have you decreased beta-mimetic use? (Rank your reasons according to order of importance)		Order of importance*					
		1st	2nd	3rd	4th	5th	All
Side-effects of the treatment	(%)	40·5	27·8	17·3	4·2	0·0	89·9
Limits in effectiveness	(%)	35·4	19·0	17·7	9·7	0·4	82·3
Improved neonatal care	(%)	13·5	18·1	21·9	19·4	0·8	73·8
Other treatments available	(%)	12·7	26·6	15·2	16·0	0·0	70·1
Other reason	(%)	3·4	0·4	1·7	2·9	1·3	9·7

n = 237.
*See footnotes to Table 1.

the French consensus conference which was held in December 1987 concluded that performing a routine ultrasound examination at 19 to 21 weeks and a second one at 31 to 33 weeks was justified (Tournaire *et al.* 1987).

Through this type of questionnaire, it is relatively easy to know whether a physician prescribes ultrasound or EFM routinely. The assessment of respondents' attitudes to beta-mimetics is less easy because numerous factors determine their prescription for an individual woman. Two previous studies have surveyed approaches to the prevention of preterm delivery, including use of beta-mimetics. If the cervix was 4 cm dilated, 87% of the obstetricians in the UK would prescribe beta-mimetics (Lewis *et al.* 1980), 88% in the Dutch-speaking part of Belgium and 78% in the Netherlands (Keirse 1984*a*); this proportion was 49% among the French obstetricians when the cervical dilatation was ≥4 cm. The comparison of these percentages needs some comment. Questions were asked in different ways in each of the surveys. The response rate of the British and the Dutch enquiries was about 50% and these might be linked to the use of beta-mimetics. These two surveys were made several years before ours, and British, Dutch and Flemish obstetricians may have decreased their use of these drugs recently as in France. Between 1985 and 1987, 51% of the French obstetricians said they had reduced their prescription of beta-mimetics. In fact the proportion of obstetricians who never used beta-mimetics prophylactically or as maintenance therapy was 27% in the Netherlands, 11% in Flanders in 1984 (Keirse 1984*b*), and 1% in France in 1987. It thus seems that there is a more active use of beta-mimetics in France and Belgium than in the UK, a difference which also exists in the use of vaginal examinations (Heringa & Huisjes 1988; Alexander 1986) and the actual words used to label threatened preterm delivery (Alexander & Slater 1987).

Our study uncovered a discrepancy between the obstetricians' attitudes and the results of the RCTs on routine ultrasound examinations, EFM and beta-mimetic drugs. Previous studies have shown this lack of relation for therapy in cardiovascular diseases in France (Boissel 1984), diuretics prescribed to pregnant women in the 1960s and the 1970s in Finland (Hemminki 1984), intrapartum EFM in the 1970s in France (Bréart 1984) and beta-mimetics prescribed in the early 1980s in the UK (Lewis *et al.* 1980), in the Netherlands and Flanders (Keirse 1984*b*).

Apart from clinical effectiveness, other benefits may be expected from a medical policy. In our survey, obstetricians mentioned women's demands and psychological effects; among the other reasons which were not specified in the tables, some respondents argued that ultrasound scans or EFM were prescribed to forestall malpractice suits against physicians. In addition, in many hospitals the number of midwives is too limited to allow continuous care without EFM. Midwives are no longer trained to care for women in labour without EFM. Moreover, midwives have more freedom for organizing their time if they use EFM and many of them are more interested in interpreting EFM tracings than in auscultation (Simkin 1986). According to Stocking (1985) one of the strongest pressures to accept an innovation is the need felt to do something. Furthermore, a new screening procedure gives midwives and obstetricians a greater sense that everything is under control (Stocking 1985). Keirse (1984*b*) also mentions the reassurance of obstetricians who prescribe beta-mimetics.

In our survey, medical reasons were more frequently reported, and more often as first reasons, than non-medical reasons. Two different types of medical reason were mentioned in the questionnaire: (i) better diagnosis with screening tests, or the tocolytic effect of beta-mimetics, and (ii) better perinatal outcome. They were distinguished because they are two stages of a medical assessment and there are no data from clinical trials which support the use of these practices for the babies whereas there is no doubt about the usefulness of both ultrasound and EFM as diagnostic tools (Falck-Larsen & Kristensen 1986; Tournaire *et al.* 1987; Benta & Thacker 1979) and the effect of beta-mimetics in reducing uterine contractility. In our survey, obstetricians mentioned diagnosis first and health benefits second as reasons for using EFM; in the same way they mentioned inhibition of contractions first and prolonging pregnancy second when prescribing beta-mimetics. These choices may be influenced by the literature. But an alternative explanation may be that obstetricians overestimate the immediate advantages of new drugs or screening tests. According to 'clinical logic', an earlier detection of fetal distress by EFM should lead to a more appropriate medical decision and to an improvement in neonatal health; in the same way a treatment which inhibits uterine contractility should prolong gestation and improve pregnancy outcome. Nevertheless, there is a gap between theory and practice. Numerous factors may explain the lack of health benefits of a new policy as has been shown in the case of beta-mimetics (Thiery 1986).

The use of ultrasound by obstetricians may differ from that suggested by the results of the RCTs because of new indications for this diagnostic modality. The randomized controlled trials were designed to assess the value of routine ultrasound in detecting intrauterine growth retardation and to estimate the gestational age more precisely. Since these trials were conducted, the technology has improved dramatically. In our study the major indication is now the detection of congenital abnormalities with a view to decreasing the incidence of major malformations at birth.

A review of studies of ultrasound published in a range of journals showed that it was viewed more favourably in French journals than in journals written in English (Ringa *et al.* 1987). This may explain the decrease in ultrasound prescription among obstetricians who were reading journals written in English. But the choice of these latter journals may express a greater awareness of obstetricians who read them about issues of the effectiveness of procedures and treatments in general.

For about 10 years, numerous papers have described severe side-effects of intravenous beta-mimetics and these effects are now well documented (Bréart & Ringa 1986; Thiery 1986). In our survey, adverse effects of beta-mimetics were the main reason given for reduced use of these drugs. Side-effects of EFM or ultrasound screening did not seem to be a prominent issue.

Our survey demonstrates the gap which exists between actual clinical practice and the results of the randomized controlled trials.

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Repeat maternal serum alpha-fetoprotein testing in antenatal screening programmes for Down's syndrome

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Summary. The risk of having a Down's syndrome term pregnancy was estimated using maternal age and the results of two maternal serum alpha-fetoprotein (AFP) tests carried out between 14 and 20 weeks gestation. The estimates of risk were derived from published data and the AFP results from nine affected and 145 unaffected pregnancies in which repeat testing had been carried out. Repeat AFP testing is unjustified in antenatal screening programmes for Down's syndrome, but if a second test happens to have been done, the appropriate estimate of risk that would be applicable when counselling individual patients depends on both results. For example a woman aged 35 years and 6 months with a first AFP level of 0·50 multiples of the normal median (MoM) was estimated to have a risk of 1:172. If a second test were done on a fresh sample and the AFP level were 0·80 MoM then the estimated risk would be 1:216 which is higher than the estimated risk of 1:353 obtained if the second test were regarded as the only result. Estimates of risk are given for maternal serum AFP results in first and second tests ranging from 0·40 to 2·50 MoM.

Antenatal screening for Down's syndrome is best performed using maternal serum alpha-fetoprotein (AFP), unconjugated oestriol, human chorionic gonadotrophin and maternal age in combination (Wald *et al.* 1988). An efficient way of combining information on the different screening variables is to calculate an individual woman's risk of having a Down's syndrome term pregnancy. A screening result is then regarded as positive if the risk is greater than or equal to a specified cut-off risk. In our previous report on screening using maternal serum AFP and age we showed how the risk could be estimated using the AFP result from the first test in a pregnancy at 14–20 weeks gestation, or from a repeat test on a second blood sample taken for reasons unrelated to the AFP level in the first sample (Cuckle *et al.* 1987) If the second sample were taken because the first yielded a low AFP level then the risk might be substantially different and would depend on both results. In this paper we assess the value of repeat testing policies and provide risk estimates for women who have two serum AFP tests.

Subjects and methods

The risk estimates in this paper relate to having a term pregnancy with Down's syndrome in the absence of antenatal diagnosis and therapeutic

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abortion. The risk is expressed as an odds ratio of 1:*u*, where *u* is the number of unaffected births that occur for each term pregnancy with Down's syndrome. The maternal age-specific risk was estimated using the formula in our previous paper (footnote to Table 1 in Cuckle *et al.* 1987).

To estimate the risk for a given maternal age and pair of AFP levels (both at 14–20 weeks gestation), the left-hand side of the maternal age-specific odds ratio is multiplied by a factor known as the likelihood ratio. We obtained the likelihood ratio from bivariate log Gaussian frequency distributions of pairs of first and second results (see Appendix I). AFP levels were expressed in multiples of the median value (MoM) for unaffected pregnancies of the same gestational age, measured in days since the first day of the last menstrual period (i.e. 'dates'). The estimates of the means and standard deviations of log AFP used to calculate the likelihood ratio were those previously estimated (footnote to Table 2 in Cuckle *et al.* 1987). The correlation coefficient between first and second log AFP values in unaffected pregnancies (R_U) was derived from 145 singleton unaffected pregnancies in which the first sample had been taken as part of routine AFP testing and the second immediately before an amniocentesis for reasons that were not related to the AFP level of the first sample. The samples had been tested between 12 and 25 weeks gestation, so the correlation coefficient applicable to 14–20 weeks gestation was estimated from the formula $R_U = C_U/S_U^2$ where C_U is the observed covariance and S_U^2 is the previously estimated variance for unaffected pregnancies at 14–20 weeks gestation (Cuckle *et al.* 1987). Nine pairs of samples from Down's syndrome pregnancies were also available. Three were from women who had a second AFP test immediately before an amniocentesis because of advanced maternal age since this was routine policy; in a further two the first sample had been collected too early for neural tube defect screening and so a second was obtained later in pregnancy, and in the remaining four pairs one or both of the sera had, by chance, been stored as part of a prospective study and only retrieved and assayed for AFP for the present investigation. Although, taken on their own, nine pairs of samples are too few to provide a reliable estimate of the extent to which the pairs are correlated, they did permit an assessment of whether the extent of correlation could reasonably be taken to be similar to that in unaffected pregnancies. In the event this was the case, so the correlation coefficient in the Down's syndrome pregnancies (R_D) was estimated from the formula $R_D = C_U/S_D^2$ where S_D^2 is the previously estimated variance for Down's syndrome pregnancies at 14–20 weeks gestation (Cuckle *et al.* 1987).

Results

Table 1 shows, for pregnancies without Down's syndrome, the median maternal serum AFP level in second tests according to the AFP level of the first test; 31% had been retested within 1 week, 83% within 2 weeks and 94% within 3 weeks. The results of the first and second tests are highly correlated, the correlation coefficient of log AFP being 0·81. The individual pairs of results for the nine Down's syndrome pregnancies are given in Table 2. Again first and second test results are correlated, the correlation coefficient of log AFP being 0·67. Excluding the result relating to the affected pregnancy with tests 13 weeks apart (number 7 in Table 2) yielded a correlation coefficient of 0·82, close to our esti-

Table 1. Pregnancies without Down's syndrome 25th, 50th (median) and 75th centile of maternal serum AFP in second tests according to the result of the first test

First AFP test (MoM)	Number tested	Second AFP test (MoM) 25th centile	Median	75th centile
<0·75	40	0·55	0·72	0·81
0·75–0·99	33	0·78	0·91	1·04
1·00–1·24	31	0·96	1·09	1·27
≥1·25	41	1·21	1·57	1·80
All	145	0·77	1·00	1·30

MoM, Multiple of the normal median at the same gestational age.

Table 2. Down's syndrome pregnancies: comparison of AFP level in first and second tests

Pregnancy	First test: Gestational age* (weeks+ days)	First test: AFP level (MoM)	Second test: Gestational age* (weeks+ days)	Second test: AFP level (MoM)
1	15+2	0·70	17+1	0·39
2	15+3	0·46	16+4	0·57
3	16+2	0·48	18+1	0·36
4	17+0	0·46	18+0	0·23
5	17+3	0·75	18+2	0·61
6	15+3	1·90†	21+3	1·55†
7	11+2	0·44†	24+2	0·88†
8	11+4	0·75†	15+6	0·88†
9	11+5	0·62†	16+2	0·69

*Calculated from the first day of the last menstrual period

†Derived from prospectively collected and frozen serum samples which were retrieved from storage and measured over a single week period.

MoM, Multiple of the normal median at the same gestational age.

mate of 0·81 for unaffected pregnancies. There is, therefore, no reason to assume that the extent to which pairs of results are correlated is different in affected and unaffected pregnancies. For the purpose of calculating likelihood ratios at 14–20 weeks gestation we have estimated the correlation coefficients to be 0·77 and 0·79 for affected and unaffected pregnancies respectively.

The differences in log AFP values between first and second tests fitted a Gaussian frequency distribution well (Fig. 1). Since a log Gaussian distribution also fits first AFP values between 0·40 and 2·50 MoM it follows that a bivariate log Gaussian distribution fits first and second test values. There were, however, insufficient data to judge whether the distributions fitted pairs of results in which the higher value was more than double the lower. Table 3 gives the likelihood ratios which apply for different combinations of first and second test results. Table 3 also shows the likelihood ratios for the first test only. The use of Table 3 can be illustrated by the following example. A woman aged 35 years and 6 months

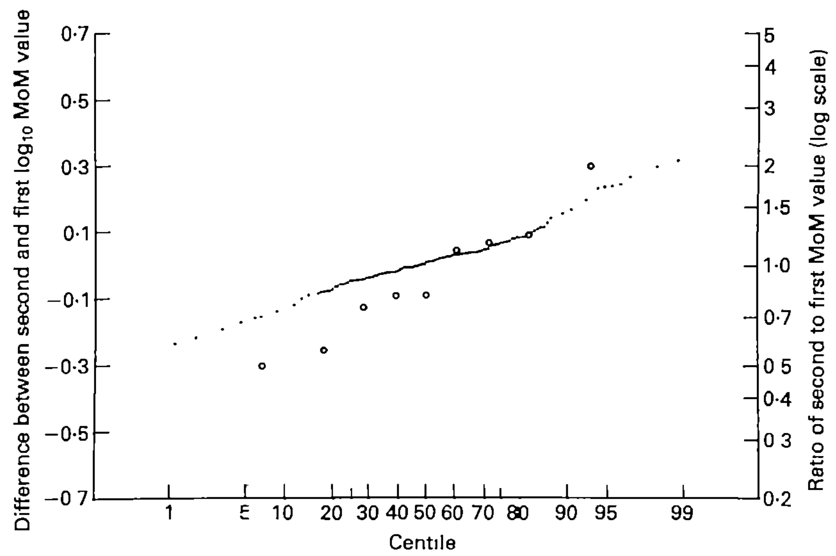

Fig. 1. Probability plot of the centiles of the difference in log AFP values between first and second tests among Down's syndrome (○) and unaffected (●) pregnancies. A straight line indicates that the difference fits a Gaussian frequency distribution

Table 3. Likelihood ratio of a Down's syndrome term pregnancy according to the AFP level in the first and second tests (all tests performed between 14 and 20 weeks gestation)

First AFP test (MoM)	No second test	Second AFP test (MoM)																						
		0·40	0·45	0·50	0·55	0·60	0·65	0·70	0·75	0·80	0·85	0·90	0·95	1·00	1·10	1·20	1·30	1·40	1·50	1·60	1·70	1·80	1·90	2·00	2·50
0·40	3·14	3·38	3·08	2·87	2·73	2·63	2·57	2·53	2·50	2·50	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
0·45	2·61	3·08	2·76	2·53	2·38	2·26	2·18	2·12	2·08	2·06	2·05	2·04	*	*	*	*	*	*	*	*	*	*	*	*	*
0·50	2·21	2·87	2·53	2·30	2·13	2·01	1·91	1·85	1·80	1·76	1·73	1·72	1·71	1·71	*	*	*	*	*	*	*	*	*	*	*
0·55	1·91	2·73	2·38	2·13	1·95	1·82	1·72	1·65	1·59	1·55	1·51	1·49	1·47	1·46	1·45	*	*	*	*	*	*	*	*	*	*
0·60	1·67	2·63	2·26	2·01	1·82	1·68	1·58	1·50	1·43	1·39	1·35	1·32	1·30	1·28	1·26	1·26	*	*	*	*	*	*	*	*	*
0·65	1·48	2·57	2·18	1·91	1·72	1·58	1·47	1·38	1·32	1·26	1·22	1·19	1·16	1·14	1·12	1·10	1·10	*	*	*	*	*	*	*	*
0·70	1·32	2·53	2·12	1·85	1·65	1·50	1·38	1·29	1·22	1·17	1·12	1·09	1·06	1·04	1·00	0·98	0·97	0·97	*	*	*	*	*	*	*
0·75	1·19	2·50	2·08	1·80	1·59	1·43	1·32	1·22	1·15	1·09	1·05	1·01	0·98	0·95	0·91	0·89	0·87	0·87	0·87	*	*	*	*	*	
0·80	1·08	2·50	2·06	1·76	1·55	1·39	1·26	1·17	1·09	1·03	0·98	0·94	0·91	0·88	0·84	0·81	0·80	0·78	0·78	0·78	*	*	*	*	
0·85	0·99	*	2·05	1·73	1·51	1·35	1·22	1·12	1·05	0·98	0·93	0·89	0·86	0·83	0·78	0·75	0·73	0·72	0·71	0·70	0·70	*	*	*	*
0·90	0·91	*	2·04	1·72	1·49	1·32	1·19	1·09	1·01	0·94	0·89	0·85	0·81	0·78	0·74	0·70	0·68	0·66	0·65	0·64	0·64	0·64	*	*	*
0·95	0·84	*	*	1·71	1·47	1·30	1·16	1·06	0·98	0·91	0·86	0·81	0·77	0·74	0·69	0·66	0·63	0·62	0·60	0·59	0·59	0·59	0·59	*	*
1·00	0·77	*	*	1·71	1·46	1·28	1·14	1·04	0·95	0·88	0·83	0·78	0·74	0·71	0·66	0·62	0·60	0·58	0·56	0·55	0·55	0·54	0·54	0·54	*
1·10	0·67	*	*	*	1·45	1·26	1·12	1·00	0·91	0·84	0·78	0·74	0·69	0·66	0·61	0·57	0·54	0·52	0·50	0·49	0·48	0·47	0·47	0·46	0·47
1·20	0·59	*	*	*	*	1·26	1·10	0·98	0·89	0·81	0·75	0·70	0·66	0·62	0·57	0·53	0·49	0·47	0·45	0·44	0·43	0·42	0·41	0·41	0·40
1·30	0·53	*	*	*	*	*	1·10	0·97	0·87	0·80	0·73	0·68	0·63	0·60	0·54	0·49	0·46	0·44	0·42	0·40	0·39	0·38	0·37	0·36	0·35
1·40	0·48	*	*	*	*	*	*	0·97	0·87	0·78	0·72	0·66	0·62	0·58	0·52	0·47	0·44	0·41	0·39	0·37	0·36	0·35	0·34	0·33	0·31
1·50	0·43	*	*	*	*	*	*	*	0·87	0·78	0·71	0·65	0·60	0·56	0·50	0·45	0·42	0·39	0·36	0·35	0·33	0·32	0·31	0·30	0·28
1·60	0·39	*	*	*	*	*	*	*	*	0·78	0·70	0·64	0·59	0·55	0·49	0·44	0·40	0·37	0·35	0·33	0·31	0·30	0·29	0·28	0·26
1·70	0·36	*	*	*	*	*	*	*	*	*	0·70	0·64	0·59	0·55	0·48	0·43	0·39	0·36	0·33	0·31	0·30	0·28	0·27	0·27	0·24
1·80	0·33	*	*	*	*	*	*	*	*	*	*	0·64	0·59	0·54	0·47	0·42	0·38	0·35	0·32	0·30	0·28	0·27	0·26	0·25	0·22
1·90	0·31	*	*	*	*	*	*	*	*	*	*	*	0·59	0·54	0·47	0·41	0·37	0·34	0·31	0·29	0·27	0·26	0·25	0·24	0·21
2·00	0·29	*	*	*	*	*	*	*	*	*	*	*	*	0·54	0·46	0·41	0·36	0·33	0·30	0·28	0·27	0·25	0·24	0·23	0·20
2·50	0·21	*	*	*	*	*	*	*	*	*	*	*	*	*	0·47	0·40	0·35	0·31	0·28	0·26	0·24	0·22	0·21	0·20	0·16

*Cannot be estimated since the higher value is more than double the lower (see text).
MoM, Multiple of the normal median at the same gestational age.

Table 4. Risk of a Down's syndrome term pregnancy according to maternal age, in years and months, at the expected date of delivery*

	Completed months											
Years	0	1	2	3	4	5	6	7	8	9	10	11
25	1:1376	1:1372	1:1367	1:1363	1:1358	1:1353	1:1348	1:1343	1:1338	1:1333	1:1328	1:1322
26	1:1317	1:1311	1:1306	1:1300	1:1294	1:1289	1:1283	1:1277	1;1271	1:1264	1:1258	1:1252
27	1:1245	1:1239	1:1232	1:1225	1:1219	1:1212	1:1205	1:1198	1:1191	1:1183	1:1176	1:1169
28	1:1161	1:1154	1:1146	1:1138	1:1130	1:1123	1:1115	1:1107	1:1099	1:1090	1:1082	1:1074
29	1:1065	1:1057	1:1048	1:1040	1:1031	1:1022	1:1014	1:1005	1: 996	1: 987	1: 978	1: 969
30	1: 960	1: 951	1; 942	1: 932	1: 923	1: 914	1: 905	1: 895	1: 886	1: 877	1: 867	1: 858
31	1: 848	1: 839	1: 829	1; 820	1: 810	1: 801	1: 791	1: 782	1: 772	1: 763	1: 753	1: 744
32	1: 734	1: 725	1: 716	1: 706	1: 697	1: 687	1: 678	1: 669	1: 660	1: 650	1: 641	1: 632
33	1: 623	1: 614	1: 605	1: 596	1: 587	1: 578	1: 570	1: 561	1: 552	1: 544	1: 535	1: 527
34	1: 518	1: 510	1: 502	1: 494	1: 486	1: 478	1: 470	1: 462	1: 454	1: 446	1: 439	1: 431
35	1: 424	1: 416	1: 409	1: 402	1: 395	1: 387	1: 381	1: 374	1: 367	1: 360	1: 354	1: 347
36	1: 341	1: 334	1: 328	1: 322	1: 316	1: 310	1: 304	1: 298	1: 292	1: 287	1: 281	1: 275
37	1: 270	1: 265	1: 259	1: 254	1: 249	1: 244	1: 239	1: 235	1: 230	1: 225	1: 221	1: 216
38	1: 212	1: 207	1: 203	1: 199	1: 195	1: 191	1: 187	1: 183	1: 179	1: 175	1: 171	1: 168
39	1: 164	1: 161	1: 157	1: 154	1: 151	1. 147	1. 144	1: 141	1: 138	1: 135	1: 132	1; 129
40	1: 126	1: 124	1: 121	1: 118	1: 116	1: 113	1: 111	1: 108	1: 106	1: 103	1: 101	1: 99
41	1: 97	1: 94	1: 92	1: 90	1: 88	1· 86	1: 84	1: 82	1: 81	1: 79	1: 77	1: 75
42	1: 73	1: 72	1: 70	1: 69	1: 67	1: 65	1: 64	1: 63	1: 61	1: 60	1: 58	1: 57
43	1: 56	1: 54	1: 53	1: 52	1: 51	1: 49	1: 48	1: 47	1: 46	1: 45	1: 44	1: 43
44	1: 42	1: 41	1: 40	1: 39	1: 38	1: 37	1: 36	1: 35	1: 35	1: 34	1: 33	1: 32
45	1: 31	1: 31	1: 30	1: 29	1: 29	1: 28	1: 27	1: 27	1: 26	1: 25	1: 25	1: 24
46	1: 24	1: 23	1: 22	1: 22	1: 21	1: 21	1: 20	1: 20	1: 19	1: 19	1: 18	1: 18
47	1: 17	1: 17	1: 17	1: 16	1: 16	1: 15	1: 15	1: 15	1: 14	1: 14	1: 14	1: 13
48	1: 13	1: 13	1: 12	1: 12	1: 12	1: 11	1: 11	1: 11	1: 11	1: 10	1: 10	1: 10
49	1: 9·5	1: 9·2	1: 9·0	1: 8·8	1: 8·5	1: 8·3	1: 8·1	1: 7·9	1: 7·7	1: 7·5	1: 7·3	1: 7·1

*Derived from the formula for risk given age in completed years by subtracting 5·5 months from the age in years and completed months and expressing the result as a decimal.

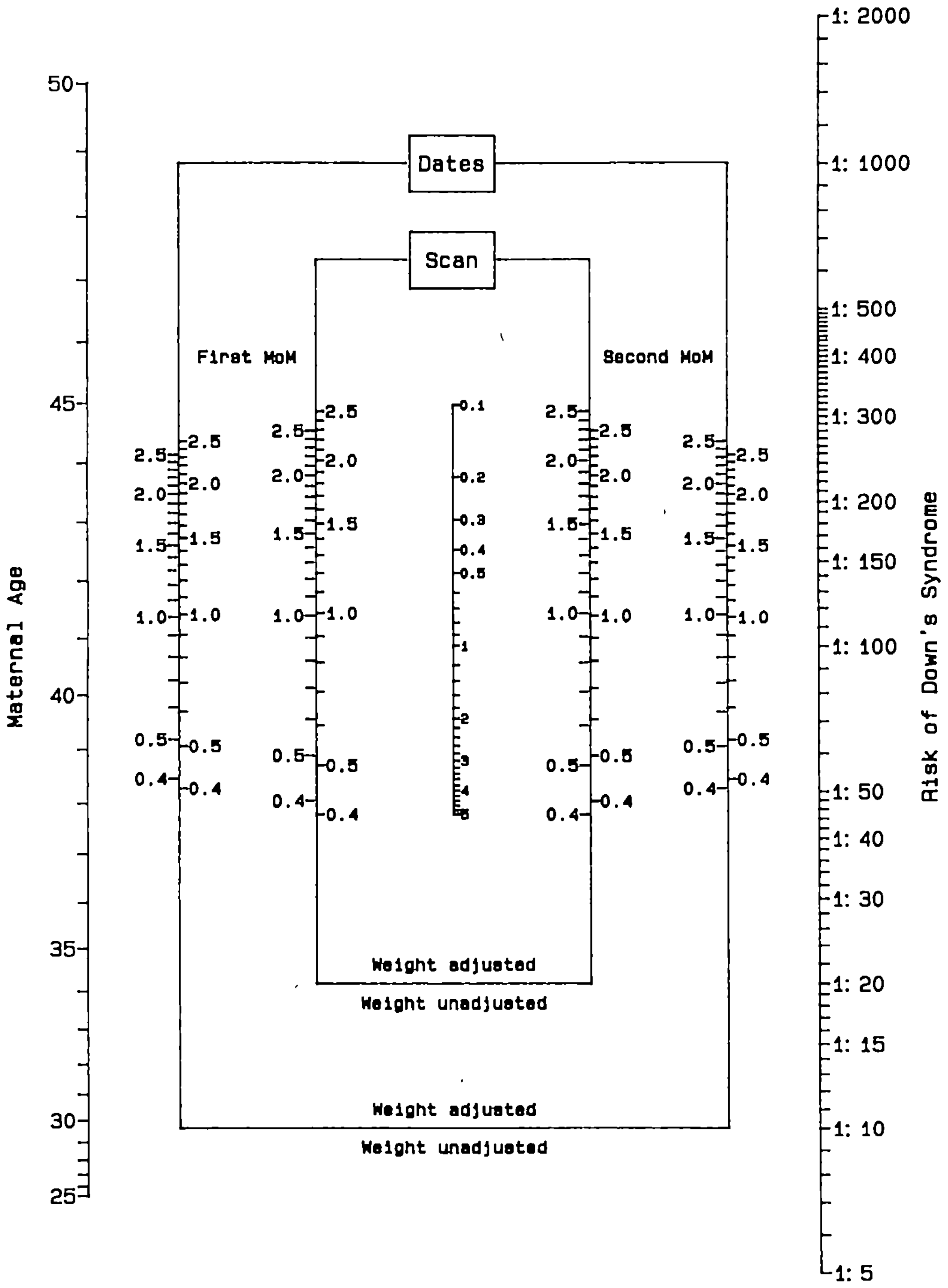

Fig. 2. Nomogram to estimate the risk of Down's syndrome expressed as an odds from maternal age (at the estimated date of delivery) and a first and second maternal serum AFP test at 14–20 weeks gestation. The nomogram is used by joining the two MoM values on the appropriate scale by a straight line and noting where the line crosses the central scale (showing the likelihood ratio). A second line is then drawn joining this point with the appropriate maternal age in years and completed months and noting where the line crosses the scale showing the risk of Down's syndrome.

Table 5. Screening for Down's syndrome at 14–20 weeks gestation: detection rate (DR), false-positive rate (FPR) and odds of an affected pregnancy if the result is positive (OAPR) according to the repeat testing policy used and the risk cut-off level used

		Risk cut-off level†																	
		1:100			1.150			1:200			1:250			1.300			1:350		
Repeat policy	Proportion repeated (%)	DR (%)	FPR (%)	OAPR	DR (%)	FPR (%)	OAPR	DR (%)	FPR (%)	OAPR	DR (%)	FPR (%)	OAPR	DR (%)	FPR (%)	OAPR	DR (%)	FPR (%)	OAPR
No repeats	0	17	0·9	1·41	23	1·7	1:61	27	2·7	1·79	31	3·8	1:97	35	5·2	1.117	39	6·7	1.137
Repeat if risk from first test is:																			
≥1.100	1	16	0·7	1.35	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
≥1·150	2	17	0·8	1:38	21	1·4	1:52	—	—	—	—	—	—	—	—	—	—	—	—
≥1.200	3		*		22	1·5	1:56	25	2·1	1:68	—	—	—	—	—	—	—	—	—
≥1:250	4		*			*		26	2·3	1:72	28	3·0	1:83	—	—	—	—	—	—
≥1:300	5		*			*			*		30	3·3	1:89	32	4·0	1:100	—	—	—
≥1:350	7		*			*			*			*		33	4·4	1:105	35	5·2	1:116
≥1:400	8		*			*			*			*		34	4·6	1.107	36	5·6	1:122
≥1.450	10		*			*			*			*			*		37	5·8	1:124

*There is no additional detection using this policy compared with the one above.

†A result is regarded as positive if the risk of a Down's syndrome term pregnancy is ≥ cut-off level, using the first test only for the 'no repeat' policy or both tests otherwise. The method used to estimate the DR, FPR and OAPR corresponding to each policy is given in Appendix II.

at her expected date of delivery has a risk of a Down's syndrome pregnancy of 1:381 (see Table 4). If the AFP level in her first test were 0·50 MoM the likelihood ratio would be 2·21 and the risk would be estimated as 1:172 (2·21×1:381) If the AFP level in the second test were 0·40 MoM, the likelihood ratio would be 2·87 and her risk would be higher (1:133), whereas if it were 0·80 MoM the ratio would be 1·76 and her risk would be lower (1:216). Interpreting the second test as the only one would yield the incorrect risk estimates of 1:121 (instead of 1:133) for 0·40 MoM and 1:353 (instead of 1:216) for 0·80 MoM.

Figure 2 is a nomogram which can be used to derive an estimate of risk for MoM values calculated using gestational age based on either an ultrasound scan examination or 'dates' (as in Table 3) and for MoM values that are, or are not, adjusted to take account of maternal weight. Instructions on how to use the nomogram are given in the legend to the figure. The estimate of risk obtained in this way will be within 10% of the exact value provided the higher of a pair of MoM values is not more than two-thirds greater than the lower. The inaccuracy arises from the need to simplify the nomogram by taking the standard deviation of log AFP in affected pregnancies to be equal to that in unaffected pregnancies. To construct the nomogram we have used the same formulae as in Tables 3 and 4 after substituting the appropriate estimates for the mean and standard deviation of $\log_{10}$ AFP from our previous paper (Cuckle *et al.* 1987), reducing the covariance to take account of a reduction in variance.

Table 5 shows the detection rate and false-positive rate, together with the odds of having a Down's syndrome term pregnancy given a positive result, according to various repeat testing policies. According to each policy, a woman has a second test if the risk, based on the first result, is greater than or equal to a specified value, and the second result regarded as positive if the risk, based on *both* results, is greater than or equal to the specified risk cut-off levels. The corresponding rates and odds if no repeat tests are performed are also given. Table 5 shows that repeat testing policies have little impact on Down's syndrome detection and are not justified in a screening programme.

Discussion

The main conclusion from our results is that there is virtually no value in a policy of offering women with positive serum AFP screening tests a second test. This, when considered with the disadvantage that such a policy would cause extra anxiety by delaying an amniocentesis, means that a policy of offering women second serum AFP tests is not justified. The conclusion confirms our earlier comments when we pointed out that because of the effect of regression to the mean a second serum AFP result will tend to be higher than the first if it is repeated because the first was low (Haddow *et al.* 1986). Consequently if the second value lies above a given AFP cut-off level this should not necessarily be regarded as a negative screening test and the patient reassured since the risk of a Down's syndrome pregnancy may still be high.

Repeat testing is often carried out as an assurance against gross errors, such as the incorrect labelling of samples, as well as to improve assay precision. In a laboratory where such errors occur so frequently that they account for, say, 10% or more of all positives, the routine retesting of women with positive results would be a solution. However, in most laboratories it is unlikely that gross errors occur as frequently as this (though we do not have a reliable estimate of the extent of the problem), and if they did, it would probably be best to correct the underlying problem.

Unjustified as it may be as a general policy, if a woman should happen to have a second AFP test her risk of having a Down's syndrome term pregnancy should be estimated using both tests, otherwise women are liable to be counselled incorrectly. Table 3 or the nomogram (Fig. 2) permit the appropriate risk to be estimated for individual patients.

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Appendix

I. Likelihood ratio for a woman with a first value (x) *and a second value* (y) *in a bivariate log Gaussian frequency distribution*

The likeihood ratio is given by the height of the bivariate log Gaussian distribution for affected pregnancies $[H_D(x,y)]$ divided by the height of the bivariate log Gaussian distribution for unaffected pregnancies $[H_U(x,y)]$.

$$H_D(x,y)=\exp[-V_D(x,y)/2]/2\pi S_D^2\sqrt{(1-R_D^2)}$$

and

$$H_U(x,y)=\exp[-V_U(x,y)/2]/2\pi S_U^2\sqrt{(1-R_U^2)}$$

where:

$$V_D(x,y)=(Z_D^2-2R_DZ_DZ'_D+(Z'_D)^2)/(1-R_D^2);$$

$$V_U(x,y)=(Z_U^2-2R_UZ_UZ'_U+(Z'_U)^2)/(1-R_U^2);$$

$$Z_D=(\log(x)-M_D)/S_D;$$

$$Z'_D=(\log(y)-M_D)/S_D;\ Z_U=(\log(x)-M_U)/S_U;\ Z'_U=(\log(y)-M_U)/S_U;$$

M_D, S_D and M_U, S_U are the means and standard deviations of values in affected and unaffected pregnancies respectively; R_D and R_U are the correlation coefficients of values between first and second tests in affected and unaffected pregnancies respectively; $\exp[x]=e^x$.

II. Estimation of the detection rate, false-positive rate and odds of Down's syndrome in women with positive results according to repeat testing policies

First the proportion of Down's syndrome pregnancies at each maternal age, in years, was calculated by applying the age-specific risk of Down's syndrome to the age distribution of maternities in England and Wales in 1981–85. The proportion of unaffected pregnancies at each maternal age was obtained by subtraction.

(i) *No repeat testing.* The detection rate for a given risk cut-off level was estimated by summing the proportions of Down's syndrome pregnancies for each maternal age when the risk based on a single maternal serum AFP result and age was equal to or greater than the cut-off (see Wald & Cuckle 1987). The false-positive rate was calculated by similarly summing the proportions of unaffected pregnancies.

(ii) *Repeat test if risk from first test ≥ specified level.* A process similar to (i) was followed but only the proportion of pregnancies at each maternal age was summed where the risk of Down's syndrome based on a first maternal serum AFP result and age was equal to or greater than the specified level and the risk based on both a first and second AFP result and age was greater than or equal to the cut-off. The proportion corresponds to the volume under the respective bivariate log Gaussian frequency distributions in Appendix I. The risk for AFP values outside the range 0·40–2·50 MoM was set equal to the risk, at the appropriate end point. For pairs of AFP levels where the higher value is more than double the lower it is assumed that a third test is done and regarded as a first test for the purposes of risk estimation.

The odds of Down's syndrome in women with positive results was estimated from the overall odds of Down's syndrome, multiplying the left-hand side by the detection rate and right-hand side by the false-positive rate.

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Maternal zinc and selenium status in pregnancies with a neural tube defect or elevated plasma alpha-fetoprotein

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Summary. Zinc and selenium status was assessed in 30 non-pregnant women, 69 women during normal pregnancy, six with a fetus with a neural tube defect (NTD) and 16 who had a raised plasma alpha-fetoprotein (AFP) but no detectable fetal abnormality. Plasma zinc and selenium concentrations were significantly reduced in the second trimester of normal pregnancy compared with non-pregnant levels. A significant decrease in concentrations of zinc in plasma and selenium in plasma and leucocytes was observed in women in the third trimester compared with women in the second trimester. Women with a fetal NTD and women with an unexplained elevation of plasma AFP had significantly lower leucocyte concentrations of zinc and of selenium. Mean values for plasma zinc, plasma and erythrocyte selenium, and for the activity of glutathione peroxidase in whole blood did not differ from those for normal pregnancy.

Most cases of neural tube defect (NTD) appear to arise from the combined action of unknown genetic and environmental factors. The importance of environmental influences is highlighted by the geographical variation in the condition and the current downward trend in prevalence (Seller 1987). Deficiencies of essential nutrients such as trace elements may be implicated in a multifactorial fashion in the production of developmental defects in humans (Hurley 1983).

Zinc is an essential trace nutrient for normal cellular growth and differentiation in all species and has an important role in the developing nervous system (Hurley 1983). Maternal zinc deficiency in rats leads to gross congenital malformations in surviving fetuses which include hydrocephalus, anencephaly and spina bifida. Even transient deficiency produces these defects if it occurs at a critical early period of development (Hurley 1981). There is evidence that zinc deficiency may be teratogenic in man (Hambidge *et al.* 1975; Hurley 1981) and it may be one environmental factor contributing to the development of NTD (Sever 1982).

Studies of zinc status in pregnancy have been hampered by the lack of a reliable index. During pregnancy there is a substantial physiological decline in plasma zinc (Swanson & King 1983), which may be reduced further by stress, and low plasma levels therefore cannot be equated with zinc deficiency. Leucocyte zinc concentrations may be a better index of extrahepatic zinc status. Levels correlate well with muscle zinc content in non-pregnant (Jones *et al.* 1981) and pregnant subjects (Meadows *et al.* 1981) and reflect zinc

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depletion in man (Prasad *et al.* 1978). Levels are not influenced by oral contraceptive use (Hinks *et al.* 1983) or steroid administration (Hinks *et al.* 1988).

The primary aim of this study was to find out whether there was evidence of maternal zinc deficiency in pregnancies in which an NTD was detected in the second trimester. Women with a normal pregnancy and women with a raised plasma alpha-fetoprotein (AFP) level, not associated with a fetal NTD, were studied for comparison. The opportunity was also taken to investigate the maternal status of another essential trace element, selenium. As an essential component of the enzyme glutathione peroxidase (EC 1.11.1.9), selenium has a key role in protecting tissues against damage from free radicals and hydroperoxides. Selenium deficiency in ewes results in a high embryonic mortality around the time of implantation (Underwood 1977), indicating an important role for this element in early gestation, but very little is known about selenium in fetal development.

The study had the approval of the joint ethics subcommittee of Southampton and South West Hampshire Health Authority and the faculty of medicine of Southampton University. Subjects gave their informed consent to the work.

Subjects and methods

Non-pregnant women

Thirty healthy non-pregnant women aged 19–36 (mean 26·3) years, who were not taking oral contraceptives, participated.

Pregnant women

Plasma AFP concentration was measured at 15–18 weeks gestation by the regional endocrine laboratory, Southampton General Hospital, as part of a routine screening service for NTD. Values were considered abnormal if they were twice the median, or greater, for the week of gestation.

Normal plasma AFP concentration and a normal pregnancy. Thirty-two women, aged 19–32 (mean 24·4) years, were studied in the second trimester (16 ± 3 weeks) and 39 women, aged 18–35 (mean 24·3) years, in the third trimester (35 ± 3·5 weeks). All of them had normal plasma AFP levels. The case notes were reviewed after delivery. One subject was subsequently excluded from each group (one had twins, the other an intrauterine death). All the other women had an uneventful pregnancy and gave birth to normal infants.

Increased plasma AFP levels or NTD. Twenty-two women, aged 17–35 (mean 25·4) years, were studied at 17·5 ± 4 weeks gestation at the time of presentation for ultrasound studies In 20 of them a raised plasma AFP had been found on screening and confirmed on a repeat blood sample collected approximately 1 week later. Multiple pregnancy or intrauterine death was excluded as a cause of the elevation. An NTD was identified in four of these pregnancies. In the two remaining women an NTD was detected by ultrasound at the booking clinic.

Laboratory measurements

Venous blood was collected between 09.00 and 11.00 hours. Leucocytes were separated using a dextran sedimentation technique (Hinks *et al.* 1982). Zinc was measured in leucocytes and plasma, and selenium in leucocytes, plasma and whole blood. The erythrocyte selenium concentration was calculated from the difference between the concentration in whole blood and plasma, taking the haematocrit into account (Lloyd *et al.* 1982). Glutathione peroxidase (GSH-Px) was measured in whole blood. Table 1 gives details of the methods and between-batch precision of analyses.

Statistical analysis

All measurements relating to zinc in plasma, selenium in plasma and erythrocytes and GSH-Px activity in whole blood were approximately normally distributed. Those for leucocyte zinc and selenium were subjected to logarithmic transformation to achieve approximate normality. The Mann–Whitney *U*-test was used to compare the leucocyte zinc and selenium levels and an unpaired *t*-test for the normally distributed results. The association between variables was assessed by calculation of Spearman's rank correlation coefficient. The log transformed means were used to calculate the geometric means for leucocyte zinc and selenium: all other data are given as arithmetic means. The 95% confidence intervals (CI) for the population means are also shown.

Table 1. Details of analyses

Analysis	Reference	Methods	Between-batch precision (CV%)
Plasma zinc	Meret & Henkin (1971);	Flame atomization and atomic	3·1
Leucocyte zinc	Hinks *et al.* (1982)	absorption spectrophotometry	3·8
Plasma selenium	Lloyd *et al.* (1982)	Hydride generation and atomic	4·9
Erythrocyte selenium		absorption spectrophotometry	5·7
Leucocyte selenium			5·9
Glutathione peroxidase	Beutler (1979)	Coupled reaction system using t-butyl hydroperoxide	7·6

Results

Normal pregnancies

Compared with non-pregnant subjects, women in the second trimester had significantly lower ($P<0 \cdot 001$) concentrations of plasma zinc and selenium (Table 2). None of the other indices measured differed significantly.

Mean plasma zinc and selenium concentrations were also significantly decreased ($P<0 \cdot 001$) in women in the third trimester compared with those in the second trimester (Table 2). The mean leucocyte selenium concentration was also significantly lower in late gestation ($P<0 \cdot 001$), but this decrease was not accompanied by a fall in the mean values for erythrocyte selenium concentration, or for whole blood activity of the selenium-dependent enzyme GSH-Px.

Pregnancies with increased maternal plasma AFP concentrations or fetal NTD

Sixteen of the pregnancies studied had no detectable fetal abnormality on ultrasound examination at the time of the study. Of the remaining six pregnancies that had a fetal NTD, anencephaly was identified in three and spina bifida in the other three. In both groups of women with increased plasma AFP levels, i.e. with and without fetal NTD, the mean concentrations of maternal leucocyte zinc were significantly lower ($P<0 \cdot 05$ and $P<0 \cdot 01$ respectively) than those in women in the second trimester of normal pregnancy. Leucocyte selenium for both these groups was also significantly reduced ($P<0 \cdot 01$ and $P<0 \cdot 05$ respectively) (Table 2). Mean values for the concentration of plasma zinc, plasma selenium, erythrocyte selenium and for the activity of GSH-Px in whole blood were not significantly different from values obtained in the second trimester of normal pregnancy. There were no significant differences for any of the indices between the six women whose fetuses had an NTD and the 16 women with a raised plasma AFP whose fetuses did not have an NTD. Plasma AFP levels and leucocyte zinc and selenium concentrations were not correlated significantly.

Complications were present in eight of the pregnancies with an unexplained elevated AFP concentration. These included miscarriage in two, preterm labour in one, and intrauterine growth retardation in four. One miscarried fetus was noted to have low-set ears at autopsy and two babies had minor congenital defects not requiring treatment: hypospadias of the glans in one and a small sacral pit in the other. Placental abnormalities were recorded in two pregnancies that miscarried and in four others. The leucocyte zinc and selenium concentrations were not significantly lower in the complicated pregnancies, compared with the other eight pregnancies in which no fetal abnormalities were reported.

None of the 22 women had malabsorptive or diarrhoeal disorders which might have predisposed to zinc or selenium deficiency One was underweight in the first trimester and had a past history of anorexia nervosa. Her nutrition may have been suboptimal. Nausea, with or without vomiting, was common in the first trimester.

Discussion

In normal pregnancy, plasma concentrations of zinc and selenium had fallen to values significantly below those of non-pregnant women by the second trimester and showed a further decrease by the third trimester. The change in

Table 2. Indices of zinc and selenium status in pregnancies with a raised plasma alpha-fetoprotein (AFP), normal pregnancies and non-pregnant women

Analysis	Non-pregnant women (*n* = 30)	Normal pregnancies		Raised plasma AFP in 2nd trimester	
		2nd trimester (*n* = 31)	3rd trimester (*n* = 38)	No fetal NTD (*n* = 16)	Fetal NTD (*n* = 6)
Plasma Zn (μmol/l)					
Mean	12·2	10·8^{W}	9·0^{U}	11·2	11·0
95% CI	11·6 to 12·8	10·4 to 11·2	8·6 to 9·4	10·2 to 12·2	10·4 to 11·6
Observed range	9·9–15·6	8·4–12·2	6·8–12·3	8·4–14·0	8·5–11·5
Leucocyte Zn (pmol/10^6 cells)					
Mean	108	105	98	88**	87*
95% CI	101 to 106	97 to 112	94 to 102	80 to 97	75 to 100
Observed range	81–153	80–173	83–141	71–146	73–104
Plasma Se (μmol/l)					
Mean	1·11	0·99^{W}	0·83^{U}	0·98	0·89
95% CI	1·07 to 1·15	0·94 to 1·04	0·79 to 0·87	0·89 to 1·05	0·80 to 0·98
Observed range	0·92–1·33	0·77–1·19	0·57–1·08	0·76–1·24	0·75–1·00
Erythrocyte Se (nmol/g Hb)					
Mean	4·86	4·85	4·56	4·64	4·39
95% CI	4·54 to 5·18	4·63 to 5·07	4·35 to 4·77	4·10 to 5·18	3·67 to 5·11
Observed range	3·87–6·75	3·55–6·71	3·55–5·95	3·04–6·65	3·58–5·12
Leucocyte Se (pmol/10^6 cells)					
Mean	1·21	1·28	1·04^{U}	1·05*	0·92**
95% CI	1·14 to 1·26	1·18 to 1·39	0·98 to 1·09	0·92 to 1·16	0·81 to 1·04
Observed range	0·96–1·53	0·86–2·14	0·77–1·66	0·76–1·51	0·80–1·03
Whole blood GSH-Px (U/g Hb)					
Mean	25·0	23·0	24·0	22·5	23·3
95% CI	22·9 to 27·1	21·8 to 24·3	22·1 to 25·9	20·0 to 25·1	21·5 to 25·1
Observed range	16·7–37·3	14·4–28·8	12·0–38·6	18·2–31·4	20·0–24·9

CI, Confidence interval for the mean

^{W} $P<0{\cdot}001$; Comparison of women in 2nd trimester of pregnancy with non-pregnant women.

^{U} $P<0{\cdot}001$; Comparison of women in 2nd and 3rd trimesters of pregnancy.

$^{*}P<0{\cdot}05$ and $^{**}P<0{\cdot}01$; Comparison of abnormal pregnancies with women in the 2nd trimester of normal pregnancies.

plasma zinc was not associated with a significant decrease in the leucocyte zinc concentration, from which it may be inferred that it did not reflect a deficiency of the element, but was merely a part of the normal physiological response to pregnancy (Swanson & King 1983).

The fall in plasma selenium, on the other hand, was associated with a significant decrease in leucocyte selenium concentration in the third trimester. If, like zinc, leucocyte selenium reflects tissue stores of the element, the decreased concentration might indicate suboptimal selenium intake. At present the selenium requirements during pregnancy are unknown. On a defined diet of 1·9 μmol (150 μg) of selenium per day, pregnant subjects had an increased conservation of selenium compared with non-pregnant controls, which was more pronounced in late gestation (Swanson *et al.* 1983). The average daily selenium intake of adults in Britain is estimated to be 0·8 μmol (60 μg) (Thorn *et al.* 1978) and an estimated safe and adequate dietary intake for adults has been defined as 0·6–2·53 μmol (50–200 μg) (National Research Council 1980). The normal selenium intake may therefore be marginally low for the demands of pregnancy. Erythrocyte selenium concentration and whole blood GSH-Px activity were not decreased significantly in the third trimester, but both have been found to be insensitive indicators of short-term selenium status in selenium depletion studies (Levander *et al.* 1983; Cohen *et al.* 1985; Thomson *et al.* 1985).

Women who had an increased plasma AFP

concentration, whether this was associated with an NTD or not, had significantly lower mean leucocyte concentrations of both zinc and selenium in the second trimester than women with normal pregnancies and a normal plasma AFP. This is a new observation which may be accounted for in two ways. The first is that the leucocyte concentrations were decreased because the intake of zinc and selenium had fallen below requirement at some time during the earlier weeks of gestation. Even a transient zinc deficiency might have contributed to the development of a NTD, if it occurred at a critical time before the closure of the neural tube (Hurley 1981), which is completed at around 25 days after conception (Morriss 1980).

The absence of a fetal NTD in pregnancies with an unaccountably raised plasma AFP and reduced leucocyte zinc concentrations could be explained by postulating that the period of zinc deficiency occurred after closure of the neural tube, or that some other essential predisposing factor, possibly genetic, was missing. It still remains, however, to account for the observed association between the raised maternal plasma AFP and low leucocyte trace element concentrations in these pregnancies. The most likely pathology underlying the raised maternal AFP is placental damage, with choriodecidual separation (Hamilton *et al.* 1985). This probably accounts also for the excess of complications reported in such pregnancies (Hamilton *et al.* 1985; Mwambingu 1985) and observed in this study It could be speculated that transient zinc (or selenium) deficiency at an early stage in pregnancy might contribute to abnormal placental development.

Since none of the women studied had diarrhoeal or malabsorptive disorders, the most likely cause of the postulated trace element deficiency would be dietary inadequacy Except for one subject who had been anorexic in the past, there was no evidence of poor nutrition in any of the women but data on intake were not available. However, even women of low parity and from a middle income group may have a suboptimal zinc intake during normal pregnancy (Hambidge *et al.* 1983) and the selenium intake from a normal diet may be marginally low in late gestation. Vomiting might precipitate a transient deficiency in the first trimester in subjects with a borderline intake.

The alternative explanation for the observations is that the lowered leucocyte zinc and selenium concentrations were merely secondary manifestations of an abnormal pregnancy and did not contribute to its production. One possibility is that a fetal product gaining access to the maternal circulation might have caused a redistribution of the two elements in the tissues. Against this proposal is the observation that the mean plasma zinc concentration did not differ significantly from that of normal pregnancy and this index is very sensitive to stress or tissue damage (Jones *et al.* 1981).

In summary, the findings of this study are compatible with the thesis that zinc deficiency in early pregnancy may be one environmental factor associated with a fetal NTD. Zinc, or selenium, deficiency may also be implicated in the feto-placental disturbance associated with an increased maternal AFP in the absence of NTD. Before accepting this hypothesis, however, further work on a larger number of subjects is needed to establish that the observed fall in leucocyte zinc was not merely a manifestation of the underlying abnormality. There is a need for more study of the importance of selenium in pregnancy.

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Measurement of cardiac output in pregnancy by thermodilution and impedance techniques

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Summary. To assess the value of impedance cardiography in pregnancy, simultaneous measurements of cardiac output were made with impedance and thermodilution techniques in 10 patients who required pulmonary artery catheterization. The methods correlated poorly ($r = 0{\cdot}17$). The discrepancy between methods was particularly pronounced in hypertensive patients. Impedance cardiography does not measure cardiac output accurately in hypertensive pregnant women.

Thoracic electrical bioimpedance techniques have been reported to measure cardiac output accurately in pregnant (Secher *et al.* 1979; Milsom *et al.* 1983), and non-pregnant subjects (Secher *et al.* 1977; Bernstein 1986*a*; Appel *et al.* 1986). Atkins *et al.* (1981) assessed longitudinal changes in cardiac output during pregnancy with an impedance technique. In contrast to previous findings, they reported a rise in cardiac output in early pregnancy which peaked at 12 weeks and then fell progressively to non-pregnant levels by 32 weeks. de Swiet & Talbert (1986) questioned the validity of these findings and they suggested that alterations associated with pregnancy violate the assumptions required by the impedance technique, and that these alterations are responsible for the diminution of cardiac output reported after 12 weeks gestation. This study was undertaken to assess the validity of impedance cardiography during pregnancy.

Subjects and methods

Ten pregnant patients requiring pulmonary artery catheterization for clinical management were studied. Simultaneous measurements of cardiac output were made in the left lateral recumbent position using thermodilution and impedance techniques. Three measurements were made by each method, and the means of the measurements were used for analysis. When multiple comparisons were made in the same woman, the first was used for this analysis. Thermodilution measurements were made by a standard technique using saline at room temperature. Impedance measurements were made using the NCOOM3 Cardiovascular Monitor (BoMed Medical), which utilizes the modified equation of Sramek *et al.* (1983). The nomogram given by Bernstein (1986*b*) was used for calculation of L value. Total thoracic impedance and dZ/dt were recorded for each measurement of cardiac output by the impedance technique. Data were analysed by coefficient of correlation.

Results

Table 1 lists the gestational age, diagnosis, and haemodynamic findings for each woman. All were in the late second or third trimesters of pregnancy. Seven patients were significantly hypertensive. Figure 1 demonstrates the relation between cardiac output measured by thermodilution and impedance techniques. The correlation coefficient was 0·17.

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Table 1. Characteristics and haemodynamic results in 10 pregnant patients

Patient	Gestational age (weeks)	Diagnosis	Thermodilution measurement of cardiac output (l/min)	Impedance measurement: Cardiac output (l/min)	Impedance measurement: dZ/dt (ohm/s)	Impedance measurement: Total fluid index (ohm)
1	26	Haemorrhage, respiratory distress syndrome	10·9	8·0	1·33	27·5
2	38	Aortic stenosis	6·2	5·8	0·81	18·6
3	25	Cardiomyopathy	6·0	7·5	0·65	32·0
4	30	Diabetic ketoacidosis, nephropathy, hypertension	8·4	5·0	0·38	13·0
5	30	Severe pre-eclampsia	9·8	6·8	0·47	14·0
6	32	Severe pre-eclampsia	10·0	2·2	0·26	15·2
7	26	Severe pre-eclampsia	7·8	3·1	0·53	21·6
8	30	Severe pre-eclampsia	5·9	3·8	0·38	29·0
9	39	Severe pre-eclampsia	10·0	7·5	1·49	29·0
10	40	Severe pre-eclampsia	10·3	5·3	0·99	21·2

Discussion

Validation studies assessing new measurement techniques against established techniques frequently employ a correlation coefficient to evaluate the data. The appropriate use of this statistical method requires that each data point be independent of all others. Published studies designed to validate the use of the impedance technique to measure cardiac output have violated these assumptions (Secher *et al.* 1977; Bernstein 1986*a*; Appel *et al.* 1986; Secher *et al.* 1979; Milsom *et al.* 1983). Table 2 lists the numbers of subjects and of measurements used in each study to calculate correlation coefficients. In each case many measurements were used from each subject. Since repeated measurements from a single subject are not independent, the conclusion of correlation between measures is not necessarily valid. In our study only one measurement was used from each individual.

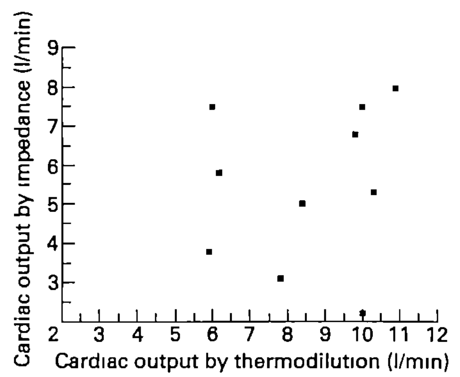

Fig. 1. Correlation between impedance and thermodilution measurements of cardiac output in 10 pregnancies $r = 0{\cdot}17$

Despite the shortcomings of the statistical analysis in previous studies, the findings reported do not suggest discrepancies in measurement of the magnitude found in our study. Given fundamental similarities in methods and equipment, differences in the subjects could account for the differences in measurements.

Bernstein (1986*b*) reported that the impedance technique significantly underestimates cardiac output in non-pregnant patients in hyperdynamic septic shock. Under these conditions dZ/dt was found to be inappropriately reduced. Bernstein (1986*b*) hypothesized that the subjects' hyperdynamic condition was associated with markedly increased myocutaneous blood flow which caused the thorax to function as a shell conductor rather than as a volume conductor. The reduced impedance in the shell resulted in a lowered dZ/dt obscuring the changes in impedance associated with systole.

Six of the seven hypertensive patients in this study were hyperdynamic. The mean cardiac output of the hypertensives measured by the impedance technique was 4 l/min less than the mean by thermodilution. In all but one patient dZ/dt was <1·0 ohm/s. The similarities of hyperdynamic condition and reduced dZ/dt suggest that haemodynamic abnormalities similar to those seen in 'warm shock' may be present in pre-eclampsia. The disruption of microvascular

Table 2. Validation studies of the impedance technique

Author	Subjects Status	 *n*	Number of measurements *n*	Correlation coefficient (*r*)
Secher *et al.* (1977)	Non-pregnant	17	94	0·86
Secher *et al.* (1979)	Pregnant	12	220	0·77
Milsom *et al.* (1983)	Pregnant	10	79	0·87
Bernstein (1986*a*)	Non-pregnant	17	94	0·88
Appel *et al.* (1986)	Non-pregnant	16	391	0·83

integrity in each condition may be associated with these alterations in regional blood flow.

The poor correlation of bioimpedance measurement with those made by thermodilution in pre-eclampsia indicates that the impedance technique should not be used in these patients. Three patients in this study did not suffer from hypertension and in these the discrepancies between measurements were much smaller. We have insufficient data to comment on the use of impedance cardiography in non-hypertensive pregnant patients, although other studies cast doubt on the accuracy of the method (de Swiet & Talbert 1986; Milsom *et al.* 1983). The analysis by de Swiet & Talbert (1986) suggests that measurements of cardiac output made by the impedance technique at 32 weeks are inconsistent with existing information regarding regional blood flow in pregnancy. They reasoned that given a uterine blood flow of 500–700 ml/min and a reduced arterio-venous oxygen difference during pregnancy, marked non-physiological alterations in regional blood flow would need to be present if cardiac output is not elevated at 32 weeks. The slope of the regression line generated in the study by Milsom *et al.* (1983) was 0·70, which also suggests an underestimation of cardiac output in pregnancy. In the light of our findings and those of others, we feel that the use of impedance cardiography in normal pregnancy should be viewed with caution. If existing technology can be improved, new methods will require rigorous assessment before general acceptance and usage.

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Blood velocities in the dorsal pedis and radial arteries during labour

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Summary. To detect evidence of aortic compression by the uterus in the supine position during labour, blood velocity in the dorsal pedis artery was recorded using Doppler ultrasound. Twenty-seven women in labour, 16 with an epidural block (epidural group) and 11 with painful contractions (non-epidural group) were studied through several contractions in the lateral and supine position. In the non-epidural group, blood velocities showed large fluctuations, typical of temperature regulation, between contractions. During contractions, velocities were reduced by 80% in both positions, most likely due to vasoconstriction caused by pain. Radial artery measurements illustrated the same fluctuations between, and reductions during, contractions. In the epidural group, blood velocities were steadily high without fluctuations between contractions, illustrating sympathetic nerve blockade. In 14 of the 16 women, velocities remained high during contractions; in the remaining two women velocities decreased, mainly in systole, during contractions in the supine but not in the lateral position without concomitant fetal heart rate pathology.

During late pregnancy and labour the uterus might compress the aorta when the woman is in the supine position. The methods used to study this phenomenon have been either blood or pulse pressure measurements from lower, and sometimes compared with upper, extremity arteries (Bieniarz *et al.* 1966; Poseiro *et al.* 1969; Goodlin 1971; Abitbol 1977; Abitbol *et al.* 1986) or angiographic studies (Bieniarz *et al.* 1968; Poseiro *et al.* 1969; Abitbol 1976). Since the uterine arteries derive from arteries peripheral to the compression site, uteroplacental circulation could be impeded (Bieniarz *et al.* 1968; Poseiro *et al.* 1969; Abitbol 1976). Fetal bradycardia during uterine contractions in the supine position is well known and has been associated with a reduction in pulse pressure in lower extremity arteries (Bieniarz *et al.* 1968; Poseiro *et al.* 1969; Goodlin 1971; Abitbol 1985; Abitbol *et al.* 1986).

Blood velocities in branches of the uterine artery decrease during contractions (Fendel *et al.* 1984; Janbu *et al.* 1985). The magnitude of the decrease is related to intrauterine pressure (Janbu & Nesheim 1987). To investigate further the haemodynamic effects of uterine contractions on the peripheral circulation and, in particular, the effects of contractions on aortic compression in the supine position, we have studied blood velocities in the dorsal pedis and radial arteries with Doppler ultrasound. We chose the dorsal pedis artery since any compression of the aorta should give recognizable effects

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here and earlier studies have been performed on lower extremity arteries (Bieniarz *et al.* 1966; Poseiro *et al.* 1969; Goodlin 1971; Abitbol 1977; Abitbol *et al.* 1986). The radial artery was studied for comparison since it should not be directly influenced by aortic compression.

Temperature regulation causes large blood velocity fluctuations in the thermoneutral zone in arteries supplying areas with arteriovenous anastomoses like the hands and feet (Burton 1939; Thoresen & Walløe 1980). Different psychological stimuli and pain produce peripheral vasoconstriction mediated by the sympathetic nerves resulting in reduced blood flow and abolition of temperature regulation (Kunkel *et al.* 1939; Abramson & Ferris 1940; Thoresen & Walløe 1980).

To study the effect of pain on the peripheral circulation during labour contractions we compared parturients who had or had not received a successful epidural block. The possibility of aortic compression was studied by examining all subjects in the lateral and supine positions.

Subjects and methods

Doppler recordings from the dorsal pedis artery were successfully obtained from 27 women in labour at term. Sixteen had received a successful epidural block and felt no pain (epidural group). The remaining 11 had either received no analgesics or only nitrous oxide and/or pethidine and had painful contractions (non-epidural group). One pregnancy in the epidural group was complicated by moderate pre-eclampsia; all others were normal. In the epidural group labour was induced in two women with oxytocin and in one with prostaglandin E_2 vaginally. In the non-epidural group labour was induced in one woman with oxytocin.

All women were in established labour with normal progress when the measurements were made at a cervical dilatation of between 2 and 9 cm. Recordings were made continuously through two to six contractions both in the supine and lateral position in all women. When in the lateral position, the upper foot was examined, and the same foot was studied in the supine position. From three women in the epidural group measurements were taken from both feet; one in the supine, one in the lateral and one in both positions. From one woman in the non-epidural group the same foot was examined in both lateral positions.

The radial artery was studied in two subjects from each group in the lateral and supine position. Continuous recordings through one to four contractions were obtained in both positions.

All measurements were made at comfortably warm room temperatures consistent with the thermoneutral zone.

Equipment

A pulsed Doppler instrument (UNIDOP) (Wille 1977; Guldvog *et al.* 1980; Hatteland & Eriksen 1981) was used to obtain Doppler signals from the dorsal pedis artery. With a 6-MHz transducer the artery was located at the dorsum of the foot at a depth of 0·5–1·0 cm. The depth was not changed during the measurement and the transducer was held steadily at an approximate angle of 45° to the artery. The signals were spectrum-analysed (fast Fourier transform) every 10 ms (Pedersen 1982) and displayed in real-time on a screen to ensure the quality of the measurement. Continuous recordings for up to 20 min were stored on tape together with ECG signals for later analysis by an ALTOS microcomputer. The time average of the instantaneous mean velocity during each cardiac cycle was calculated, estimating an angle of insonication of 45°.

Recordings from the radial artery were made at the wrist. A 6-MHz transducer was held at an approximate angle of 45° with the artery, measuring at a depth of 0·5–0·8 cm.

A Corometrics cardiotocograph was used to record FHR, either transabdominally or with a fetal scalp electrode. In our department, FHR is not regularly recorded continuously in normal labours unless the woman has received an epidural block. Thus, FHR tracings were available from 15 women in the epidural group and seven in the non-epidural group.

Contractions were recorded either by an external sensor connected to the cardiotocograph or as indicated by the woman.

Results

Non-epidural group

Doppler recordings were successfully obtained during 53 painful contractions from 11 women. Between contractions blood velocities showed large and rapid fluctuations typically seen in these vessels at comfortably warm room tem-

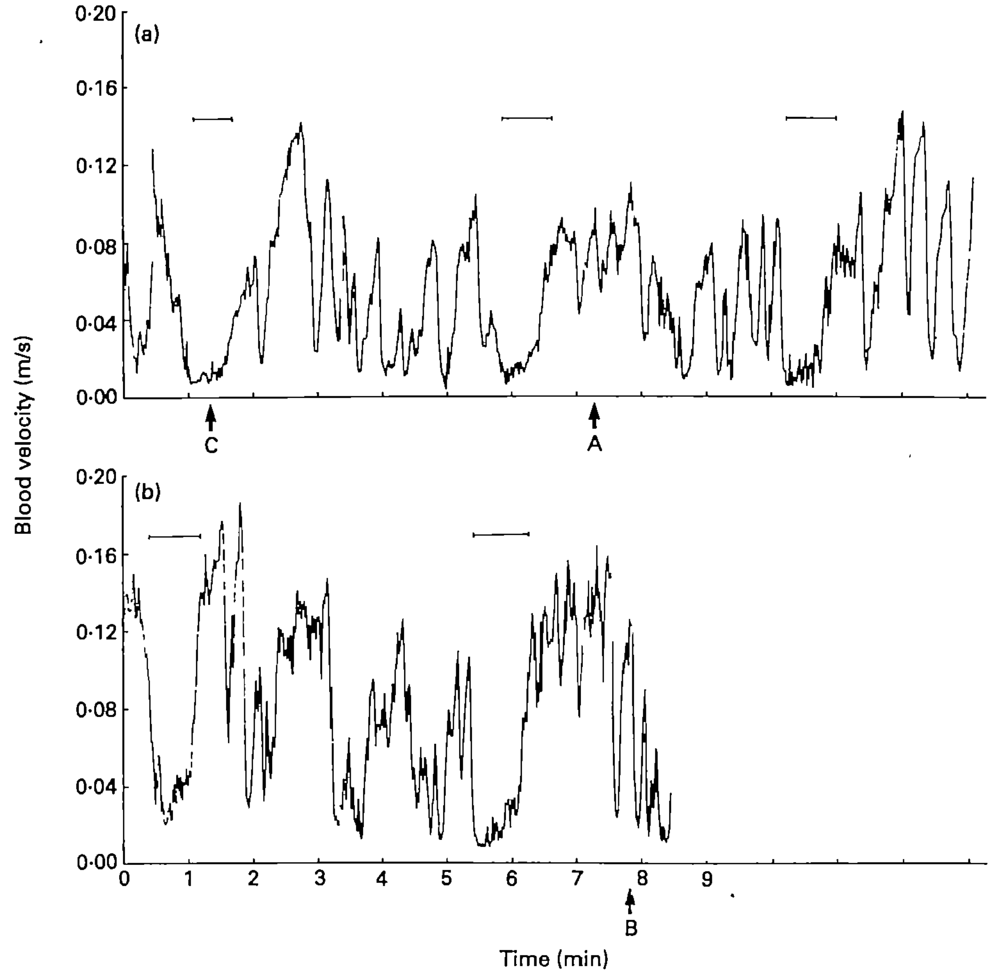

Fig. 1. Typical blood velocity recordings from the doral pedis artery during several minutes in the supine (a) and lateral position (b). Both panels are from the same woman in the non-epidural group. Contractions are marked with horizontal bars (——) as indicated by the woman. A, B and C mark the time at which the waveform pictures shown in Fig. 2 were taken.

peratures (Fig. 1). The medians of the high and low velocity periods of the fluctuations were 0·10 m/s (range 0·06–0·20 m/s) and 0·03 m/s (range 0·01–0·06 m/s), respectively. The velocities fell during contractions both when the subject was in the lateral and supine position (Fig. 1). The median reduction was 80% (range 67–86%); lateral 82% (range 67–86%) and supine 77% (range 68–83%). Reductions were calculated from the median of at least two consecutive high velocity periods just before or following the contraction. The velocity decreases were of the same magnitude as during the low velocity periods between contractions; but they lasted for the whole duration of the contraction.

Doppler waveforms representative of high velocity periods were characterized by continuous forward flow through diastole and high systolic values (Fig. 2A). During low velocity periods the major changes were seen in diastole with initial back-flow indicative of peripheral vasoconstriction (Fig. 2B). Doppler waveforms during a contraction-induced velocity reduction also show the main changes during diastole (Fig.

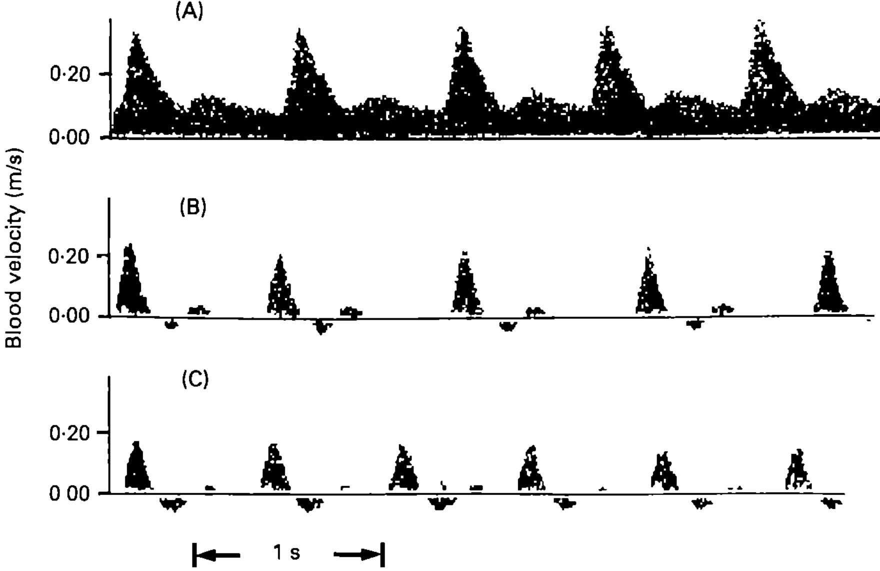

Fig. 2. Doppler spectra from the dorsal pedis artery velocity recording in Fig 1, from one typical woman in the non-epidural group. A, B and C refer to Fig 1, marking the time at which the waveform pictures were taken. (A, B) Waveforms from high (A) and low (B) velocity periods between contractions. (C) Waveforms at the peak of a contraction.

2C), and the waveforms could not be distinguished from those seen during low velocity periods between contractions.

Studies on the same foot in both lateral positions in one subject showed no differences related to position.

FHR recordings, available from seven subjects, were all normal.

Epidural group

Doppler recordings were successfully obtained during 131 contractions from 16 women. Between contractions the velocities were steadily high without fluctuations (Fig. 3). The median velocity (0·15 m/s; range 0·10–0·28 m/s) was 50% higher than the median of the high velocity periods between contractions in the non-epidural group. In 14 subjects velocities and waveforms remained unchanged during contractions in both positions. The Doppler spectra showed continuous forward flow in diastole and high systolic peaks. Velocities and waveforms from one typical subject are illustrated in Fig. 3.

In the remaining two women velocities fell by a median of 60% (range 55–67%) during all contractions in the supine but not in the lateral position (Fig. 4). This phenomenon could be demonstrated repeatedly by turning the subject. The major spectrum changes during the supine contractions were reductions in systole while a reduced but continuous diastolic flow persisted (Fig. 5).

Recordings from the dorsal pedis artery on both feet, made from three women, showed no differences between the feet in either position.

FHR was monitored in 13 of the 14 women who had no changes in blood velocities in either position. Six of these 13 women had FHR decelerations during contractions. One of these had late decelerations in both positions suggesting fetal asphyxia. Because of this she was later delivered by caesarean section. Three others had variable decelerations, one in the supine position only; all three were delivered vaginally and two of the infants had a nuchal cord. Two women had early decelerations and normal vaginal deliveries. Of the six infants with FHR decelerations, five had Apgar scores above 7 and 9 at 1 and 5 min and the sixth, who had a nuchal cord, had Apgar scores of 2 and 9

FHR was monitored in both women who had velocity reductions during contractions in the supine position only. Both had normal FHR recordings and uneventful deliveries.

Radial artery

Doppler recordings were successfully obtained during 16 contractions from four women.

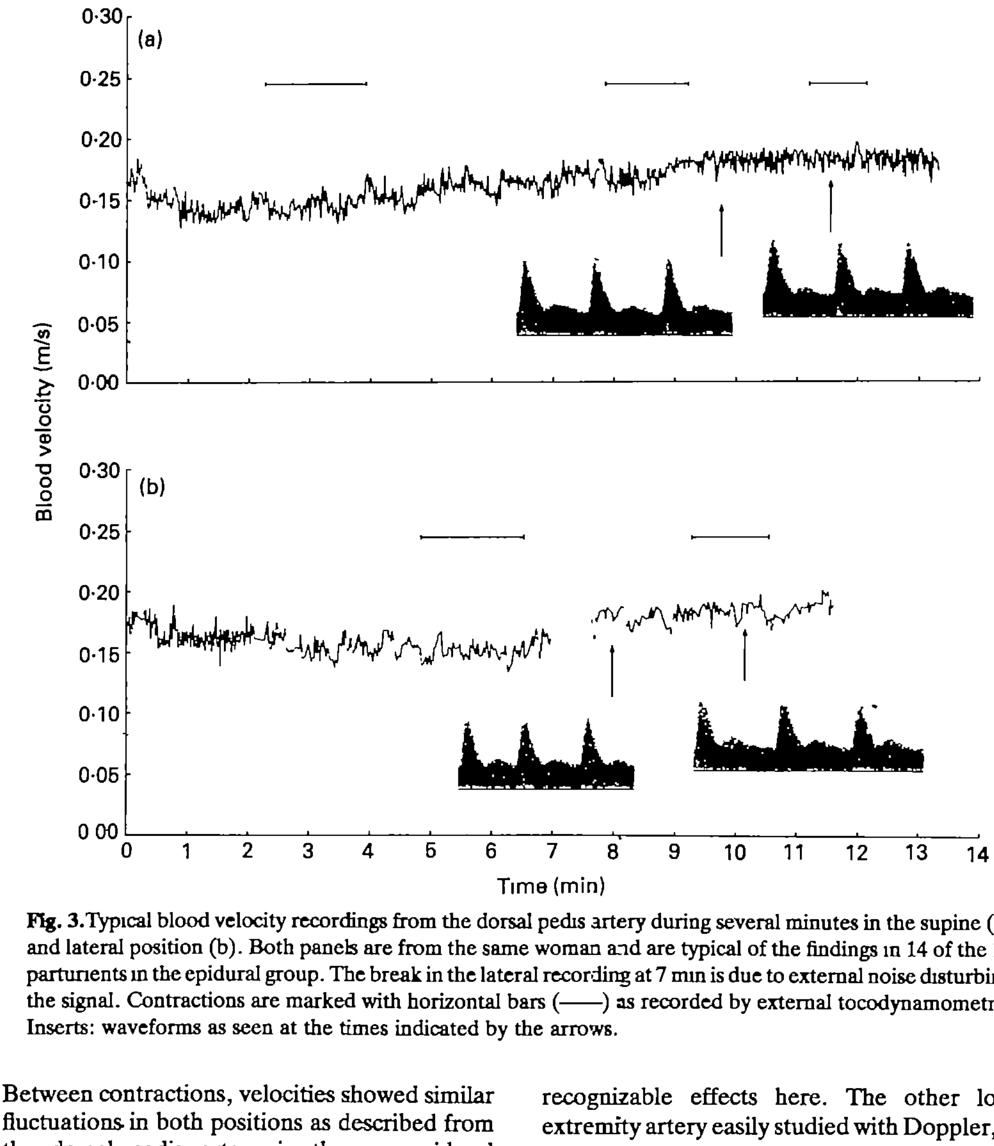

Fig. 3. Typical blood velocity recordings from the dorsal pedis artery during several minutes in the supine (a) and lateral position (b). Both panels are from the same woman and are typical of the findings in 14 of the 16 parturients in the epidural group. The break in the lateral recording at 7 min is due to external noise disturbing the signal. Contractions are marked with horizontal bars (——) as recorded by external tocodynamometry. Inserts: waveforms as seen at the times indicated by the arrows.

Between contractions, velocities showed similar fluctuations in both positions as described from the dorsal pedis artery in the non-epidural group. This pattern was not altered by an epidural block.

During contractions in the non-epidural group velocities in the radial artery decreased by a median of 57% (range 70–54%), irrespective of position. In the epidural group the velocity fluctuations were not influenced by the contractions in either position. Figure 6 shows radial artery velocities during painful contractions in the lateral position (b) and during painless contractions (epidural) in the supine position (a).

Discussion

We chose the dorsal pedis artery for this study since any compression of the aorta should give recognizable effects here. The other lower extremity artery easily studied with Doppler, the femoral artery, could not be used because of the post-contraction hyperaemia resulting from even weak contractions of lower extremity muscles (Wesche 1986).

An angle of insonication of 45° was used during velocity calculations. The course of the dorsal pedis artery at the dorsum of the foot is almost parallel to the skin. This enables a satisfactory visual control of the angle by keeping the transducer at 45° to the skin. As long as the depth is unchanged during a continuous good measurement, the angle must also be unchanged otherwise the quality of the Doppler spectra would deteriorate. Furthermore, the results of this study mainly concern velocity changes which

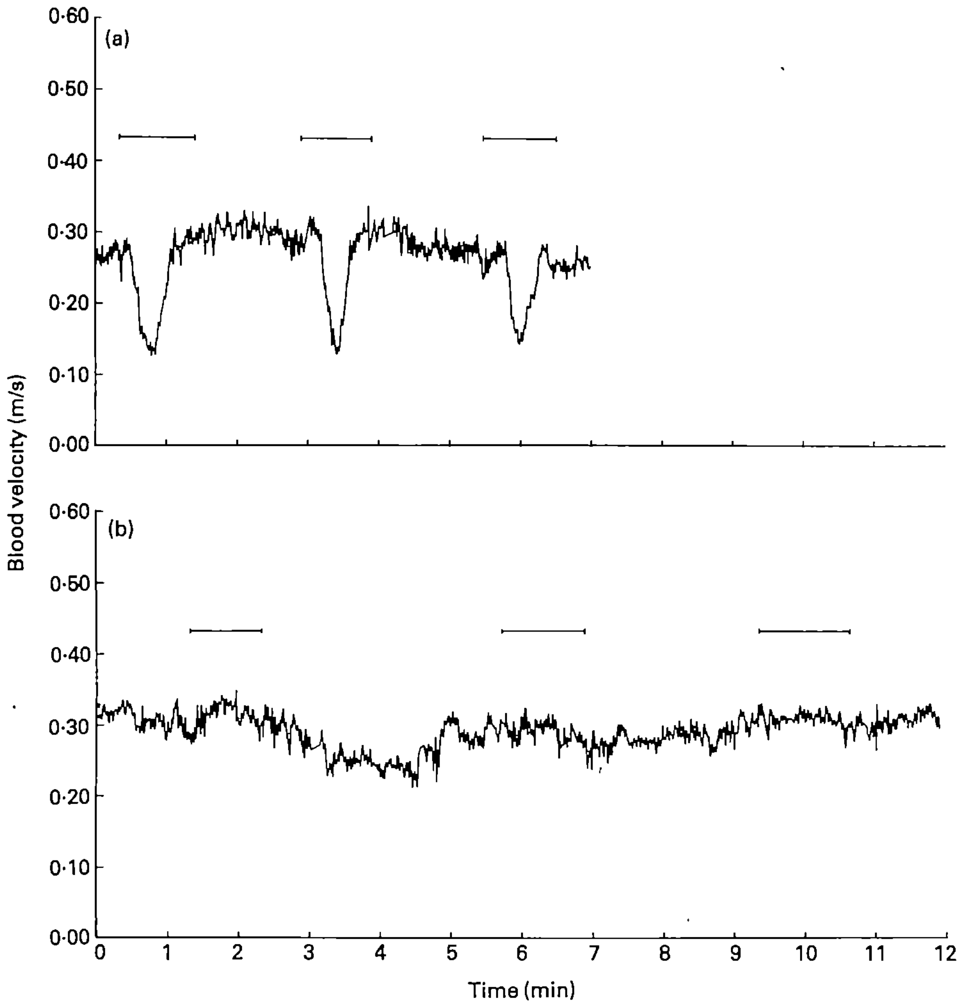

Fig. 4. Typical blood velocity recordings from the dorsal pedis artery from one of the two subjects in the epidural group who had velocity reductions during contractions in the supine position (a) but not in the lateral (b) Contractions are marked with horizontal bars (——) as recorded by external tocodynamometry. For waveforms see Fig. 5.

eliminate angle inaccuracies as long as the angle is unchanged. When considering absolute velocity values, differences between subjects are not necessarily due to corresponding variations in flow but rather to individual differences in the diameter of the vessel (Wesche 1986; Eriksen 1987).

The vascular beds of the hand and foot are known to participate in temperature regulation by periodically opening and closing arteriovenous anastomoses under nervous control (Burton 1939; Thoresen & Walløe 1980). This causes large changes in blood flow in more proximal arteries. The velocity fluctuations found in the dorsal pedis artery between contractions in the non-epidural group and in the radial artery in both groups are very similar, both in amplitude and frequency, to those observed in non-pregnant subjects (Thoresen & Walløe 1980).

Pain is known to cause constriction of arterioles, mediated by the sympathetic nerves (Kunkel *et al.* 1939; Abramson & Ferris 1940). Hence, in the non-epidural group pain most likely produces the position-independent velocity drop noted during contractions. The

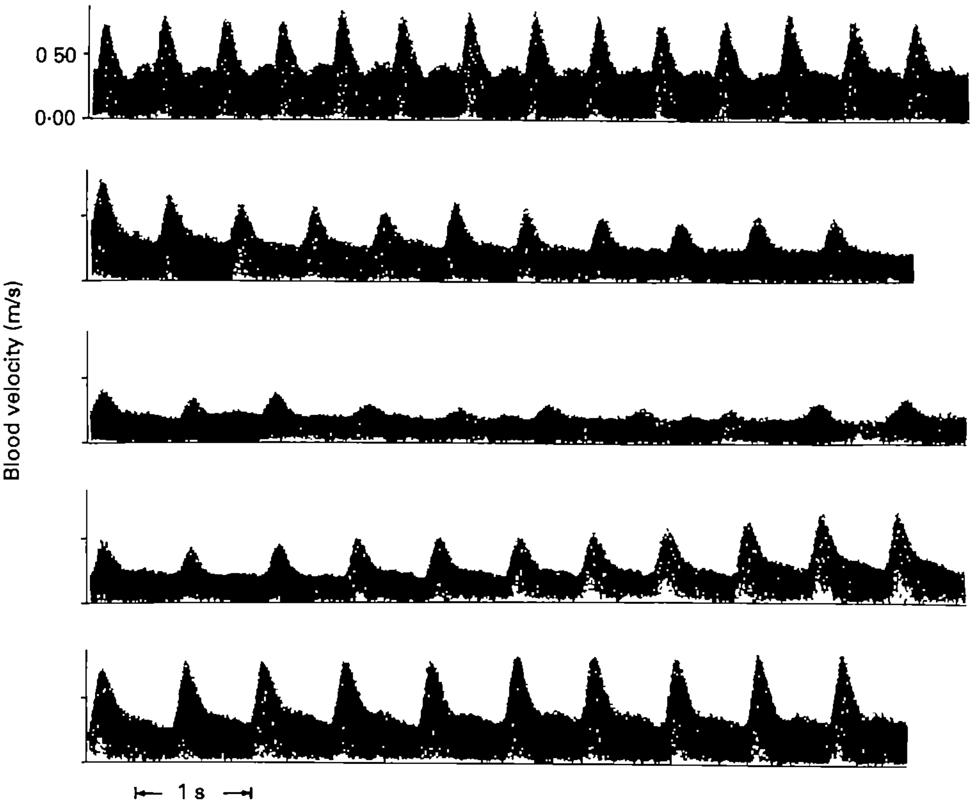

Fig. 5. Waveforms as seen while recording from the dorsal pedis artery during the second contraction in the supine position in Fig. 4; from one of the two subjects in the epidural group who showed velocity reductions in the supine position only. The recording is continuous, but broken up into five lines for practical reasons

pain response is a generalized reaction and was, accordingly, also recorded from the radial artery. When pain was relieved by an epidural block, only the temperature-regulating fluctuations in the radial artery remained.

In the epidural group no velocity fluctuations were found in the dorsal pedis artery between contractions. Since epidural anaesthesia blocks sympathetic nerves, vasoconstriction is inhibited. The resulting continual vasodilatation explains the high unchanging velocities. This is in accordance with reports of increased leg blood flow, measured by venous occlusion plethysmography, during epidural anaesthesia (Bonica *et al.* 1970; Modig *et al.* 1980; Sjögren & Wright 1972) and with Doppler studies reported by Poikolainen & Hendolin (1983) who found an increase in femoral vein blood velocity following epidural block. Wright & Cousins (1972) reported significantly increased skin temperature of the foot after epidural block.

In the epidural group the painless contractions and the sympathetic nerve blockade explain the absence of velocity reductions similar to those seen in the non-epidural group. But two women had marked mean velocity reductions during all contractions in the supine position only. The accompanying waveform changes, consisting mainly of systolic reductions, could be explained by compression of the aorta by the contracting uterus. This would reduce systole and pulse pressure distal to the compression site, as illustrated by Abitbol (1977) who externally compressed the aorta in postpartum women. These waveform changes are clearly different from those seen during low velocity periods and painful contractions in the non-epidural group.

Vena caval compression is well known to occur in some pregnant women (supine hypotensive syndrome) with possible effects on the uteroplacental circulation. Compression of the vena cava would cause high forward flow in systole and marked backflow in diastole in peripheral arteries draining into the vein. This vascular

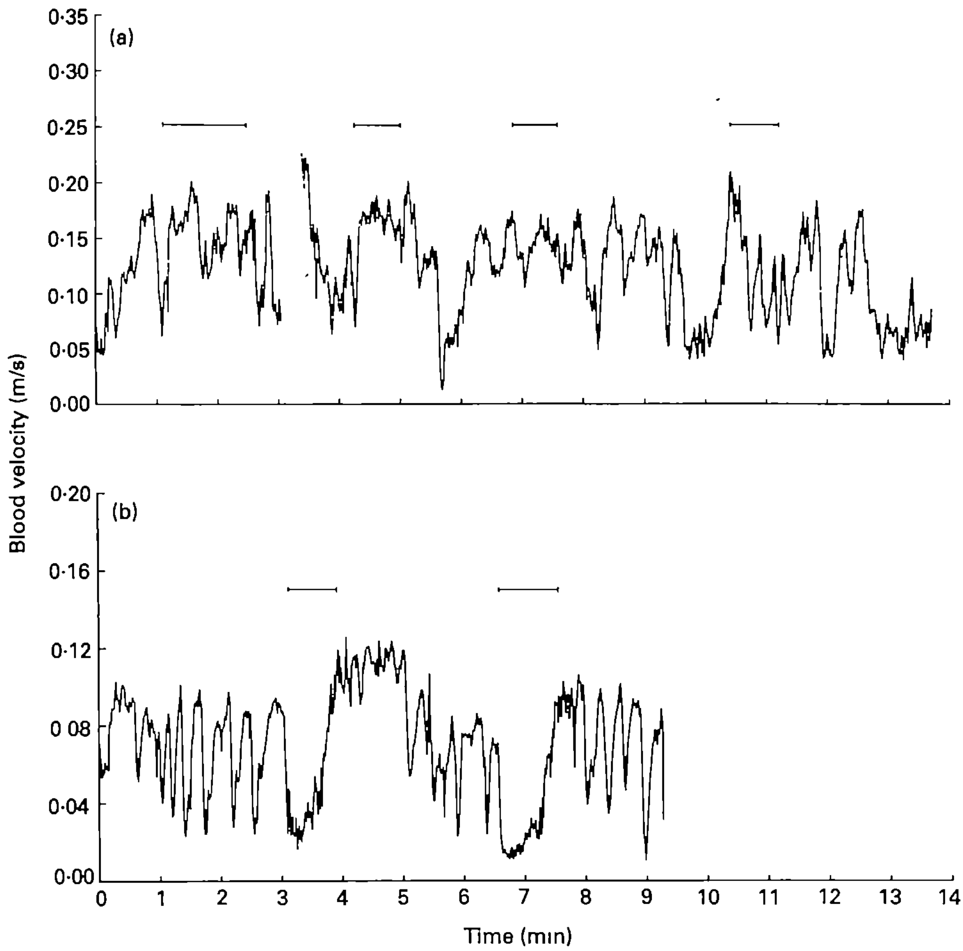

Fig. 6. Blood velocity in the radial artery. (a) Supine recording from one subject in the epidural group. The break in the recording at 3 min was caused by movement of the hand. (b) Lateral recording from one subject in the non-epidural group Contractions are marked with horizontal bars (——) as recorded by external tocodynamometry (a) or as indicated by the parturient (b).

phenomenon can easily be demonstrated by compressing an extremity vein while measuring with Doppler on a distal artery. In the present study the waveform changes described from dorsal pedis recordings in two supine parturients are not compatible with vena caval compression. As seen in Fig. 5, systole is markedly reduced while continuous diastolic flow persists. Figure 5 also shows that heart rate is reduced during the contraction. This is not in agreement with vena caval compression since the latter would reduce venous return to the heart which would cause tachycardia, mediated by the baroreceptor reflex. Hence, it is possible to conclude that the velocity and waveform changes seen in these two women are mainly the effects of aortic compression. The other 14 women in the epidural group showed no waveform changes during contractions in either position; hence, no indication of aortic or vena caval compression.

Compression of the aorta during supine contractions in normotensive subjects, indicated as reductions in femoral artery blood pressure, was found in 40% by Abitbol (1977), in 28% by Poseiro *et al.* (1969) and in none of three by Bieniarz *et al.* (1966). Goodlin (1971) described a reduction in hallux pulse pressure during supine contractions in 37% of the parturients with caudal anaesthesia and in 19% of those without; he tentatively explained this discrepancy between the two groups as an effect of possible hypotension in the caudal anaesthesia group. Perhaps the more likely explanation is vasoconstriction caused by pain in the other group, since this would counteract the effect of aortic compression on hallux pulse height. In the present study the frequency of blood velocity reductions during painless supine contractions was 13% (95% CI 2 to 40%) which is in reasonable accord with the other publications cited above.

Harmful effects on the fetus of aortic compression are not always apparent. In the series studied by Goodlin (1971) FHR became abnormal in 33% of the parturients who remained in the supine position after pulse pressure reductions during contractions were established. In our study we found no adverse FHR features in either position in the two women who had velocity reductions in the dorsal pedis artery during supine contractions. Late FHR decelerations were present in one and variable decelerations in three women who did not have supine velocity reductions. In one of them, with a nuchal cord, variable decelerations occurred in the supine position only. Considering the aetiology of FHR abnormalities, the importance of aortic compression during contractions is not precisely defined. In two earlier studies (Janbu *et al.* 1985; Janbu & Nesheim 1987) we found blood velocity reductions of 50–60% in uterine arteries during contractions. This is most probably caused by the compression of traversing smaller arteries during the myometrial contraction. Normally FHR is not affected by this. The result of an additional compression of the aorta is not obvious and might be of minor importance compared to the large reduction in uterine blood flow invariably occurring during contractions

Abitbol *et al.* (1986) investigated the nonstress test in pregnant women and showed that a reactive test in the lateral position with a nonreactive test in the supine position coincided with a reduction in femoral artery and hallux capillary pulse pressure. When followed through labour, 19 of the 21 patients who had this pattern showed FHR abnormalities only, or more severely, in the supine position. This finding, together with our results and those reported by Goodlin (1971), could be explained by postulating that a persistent smaller compression of the aorta between contractions could reduce fetal oxygenation, and the subsequent contraction, which always reduces uteroplacental blood flow markedly (see above), could cause asphyxia in the slightly hypoxic fetus. If the aorta is not compressed between contractions, compression during contractions could be of minor importance.

The present study shows that aortic compression during contractions, giving a reduction in dorsal pedis blood velocities, usually does not occur. When it does occur it is not necessarily accompanied by FHR pathology. During painful contractions both upper and lower extremity artery recordings demonstrate peripheral vasoconstriction. This response is abolished after pain relief by an epidural block, which also eliminates temperature-regulating fluctuations in the lower but not upper extremity arteries. Hence, when studying aortic compression by measuring pulse pressure in lower extremity arteries, attention should be given to the possibly interfering effects of pain and temperature regulation.

Acknowledgments

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Aldosterone is secreted intermittently during pregnancy

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Summary. Saliva aldosterone concentration was measured in samples collected at hourly intervals from healthy pregnant women (approximately 26 and 36 weeks gestation) who were going about their normal daily activities, and from some women hospitalized for disorders of pregnancy. In the healthy women diurnal saliva aldosterone fluctuated considerably, the highest values being 2–22 times the lowest on a given day. Because of the known correlation between saliva and plasma aldosterone concentrations we believe that the fluctuating salivary level is indicative of fluctuating plasma levels and that this is due to the intermittent secretion of aldosterone. The rate of decline of saliva aldosterone from peak levels indicated a half life ($t_{\frac{1}{2}}$) of 72 (SD 31) min which was not significantly different from that in non-pregnant subjects. The temporal pattern of saliva aldosterone suggests an enhanced response of the zona glomerulosa to the factors that cause aldosterone secretion to fluctuate in non-pregnant subjects, rather than the development of a more potent stimulus to the zona glomerulosa during pregnancy. In addition to hour-to-hour variation there is also substantial day-to-day variation, so that estimation of aldosterone in a single sample of saliva or plasma is of little value during pregnancy. The mean diurnal aldosterone concentration can be estimated from five saliva samples so this measurement presents a convenient technique for the assessment of aldosterone status in pregnancy. In contrast to healthy pregnancy, a patient with pre-eclampsia at 39 weeks gestation showed no elevation of saliva aldosterone above non-pregnant levels at any time during the day.

It has long been known that the rate of secretion of aldosterone is increased during pregnancy (Jones *et al.* 1959) while the proportion of circulating aldosterone bound to plasma proteins (Dunn *et al.* 1981) and the metabolic clearance rate (Tait *et al.* 1962) are unaltered. These factors account for the well-described increase in plasma aldosterone concentration during pregnancy (Weir *et al.* 1975; Dux *et al.* 1984; Karlberg *et al.* 1984; Few *et al.* 1986*a*). No satisfactory explanation of the increase in aldosterone secretion during pregnancy has been offered, though it has been suggested that it represents a response to the anti-aldosterone effect of progesterone (Landau & Lugibihl 1958; Sundsfjord 1971; Oparil *et al.* 1975).

Most investigators have implicitly assumed

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that aldosterone levels are elevated continuously during pregnancy, but while the circadian rhythm of cortisol has been comprehensively investigated during pregnancy (Nolten *et al.* 1980; Cousins *et al.* 1986), no comparable study on aldosterone has been reported. We anticipated that knowledge of the diurnal pattern of aldosterone level might help to clarify the clinical significance of the elevated levels of aldosterone seen during pregnancy.

Investigations of this nature usually utilize a series of blood samples collected through an indwelling catheter which requires that they are conducted in a clinical setting, with which the subject may not be familiar. It is not known to what extent psychosomatic effects of such an environment might influence the results. We have therefore chosen to utilize saliva for estimating the aldosterone levels as this has been shown to correlate well with plasma levels both in the non-pregnant (Few *et al.* 1984, 1987) and pregnant conditions (Few *et al.* 1986*a*). Subjects were thus able to collect samples with minimal inconvenience while going about their normal daily activities.

Subjects and methods

Healthy pregnant women were asked to collect saliva samples 'every hour, on the hour' throughout a day of normal activity with the first sample being collected while still in bed. Most subjects had given up work, and those who had not, collected at the weekend. In addition, some samples were collected from patients admitted to hospital for disorders of pregnancy.

Saliva was collected by dribbling into 7-ml plastic bottles and either frozen within a few hours or transported to the laboratory the next day for freezing After thawing, debris was removed from the saliva by centrifugation. Aldosterone concentration was determined by a micro-modification (Few *et al.* 1986*b*) of our original method (Few *et al.* 1984). Glucocorticoids (cortisol+cortisone) were measured as described previously (Few *et al.* 1986*b*) except that cortisol-3-(0-carboxy-methyl)oximino-2-[^{125}I]-iodohistamine (prepared by the method of Nars & Hunter 1973) was used as the ligand instead of [^{3}H]cortisol. This permitted the use of 20-μl samples of saliva and standards. In this assay cortisone does not cross-react so strongly (70% compared with 100%) therefore the measured values using the iodine-labelled ligand (y) are about 80% of those obtained using the tritiated ligand (x). The two values are highly correlated ($y = 0{\cdot}667x+2{\cdot}0$; $r = 0{\cdot}93$; $n = 41$).

Progesterone was assayed by extracting 0·5 ml saliva with 3 ml petroleum ether (boiling range 40–60°C). The extract was evaporated to dryness and the residue was redissolved in 400 μl methanol. Duplicate 100-μl aliquots of the saliva extracts and standards (4–2000 pg/100 μl) were evaporated to dryness in 10·5×63·5 mm polystyrene assay tubes. Radioimmunoassay was performed using [^{3}H]progesterone as ligand, an antibody to 11α-succinoxy-progesterone BSA and dextran-charcoal to separate free and bound fractions.

The half lives ($t_{\frac{1}{2}}$) of aldosterone and glucocorticoids were calculated when the steroid concentration decreased for ≥2 h using the expression $t_{\frac{1}{2}} = \log 2/k$ where k is the slope of the regression line of log concentration against time. Data were used only if the correlation coefficient between log concentration and time was greater than 0·9.

The percentage variation (%V) was used as an index of the degree of the diurnal fluctuation of the concentrations of aldosterone, glucocorticoids and progesterone in saliva. This represents the average (absolute) difference between the observations and the mean expressed as a percentage of the subject's mean; it is calculated from the expression

$$\%V = \frac{\sum(\bar{x}-|x|)}{n} \times \frac{100}{\bar{x}}$$

where x and $\bar{x}$ are individual and diurnal mean values for saliva steroid concentrations respectively (Cousins *et al.* 1986).

Results

Table 1 summarizes the aldosterone and glucocorticoid data on all the subjects we have investigated. Figure 1 shows the diurnal pattern of saliva aldosterone before pregnancy and at 26 and 36 weeks of pregnancy in subject 1. Figure 2 compares the patterns of saliva aldosterone and glucocorticoids in subject 2 at 28 weeks measured over 2 consecutive days. In most subjects, over the whole day, glucocorticoids were negatively correlated with time ($r > 0{\cdot}7$) reflecting the well-known circadian rhythm of cortisol secretion. No comparable correlation was detected between saliva aldosterone and time.

Table 1. Range and variability of saliva aldosterone and glucocorticoid concentrations in pregnancy

				Aldosterone (pmol/l)			Glucocorticoids (mmol/l)		
Subject	Gestation (weeks)	Time	No. of samples	Range	Mean	Per cent variation	Range	Mean	Per cent variation
Normal pregnancy									
	0	0600–2200	17	18–132	53	61	3·5–56	23·0	37
1	26	0800–2100	12	94–700	378	45	9·0–29·0	18·1	27
	38	0800–2200	14	82–1000	419	36	14·5–36·0	24·8	23
	PP*	0850–2345	11	0–182	48	50	0–15·0	8·5	53
	PP	0925–2320	11	28–196	89	49	0–17·0	9·3	48
2	28	0800–2400	16	65–1015	367	71	9·8–32·5	20·6	31
	28	0800–2300	16	85–1125	451	53	6·9–36·3	17·4	38
	38	1000–0030	15	110–995	345	71	20·7–44·2	27·6	17
	38	1015–0015	15	130–1200	571	54	23·1–43·9	31·4	18
	26	1000–2200	12	87–772	397	40	9·0–21·0	13·3	28
3	26	0630–2245	16	34–764	280	61	7·0–47·0	17·6	36
	36	0840–2300	14	175–975	490	32	9·0–31·0	16·7	27
	36	0930–2300	14	287–1085	668	28	8·0–26·0	19·1	22
4	36	0745–2145	9	370–805	521	28	15·4–27·5	20·0	17·5
5	36	0815–0030	16	214–1145	774	33			
6	26	0800–2200	11	60–412	204	57	11·3–24·5	16·3	120
7	36	0800–2200	12	105–970	319	69	6·0–43·0	16·9	42
	37	0700–2200	13	75–980	247	72	6·0–22·0	15·8	31
8	26	0615–2230	18	42–739	381	48	5·4–28·5	15·0	27
9	34	0630–0030	18	116–964	387	44	10·0–24·0	14·0	22
Pre-eclampsia									
10	35	0615–2340	18	32–116	75	22	9·5–22·3	15·6	19
Coarctation									
11	31	0800–2100	11	138–1320	514	45	5·5–37·5	15·7	49
Twin pregnancy									
12	32	1030–0045	14	26–557	227	52	3·0–10·8	7·1	28

* PP = 6 weeks postpartum

The degree of fluctuation (%*V*) of aldosterone was invariably greater than that of the glucocorticoids (Table 1); moreover, not only did aldosterone show greater variability but the pattern was different. Whereas most of the fluctuation in the glucocorticoids was attributable to the circadian rhythm of cortisol secretion, that of saliva aldosterone was not time related. Because

Table 2. Half life ($t_{\frac{1}{2}}$) for saliva aldosterone and glucocorticoid concentrations in pregnant (>24 weeks) and non-pregnant women

	Half life (min)							
	Aldosterone				Glucocorticoid			
Patient group	*n*	Mean	(SD)	Range	*n*	Mean	(SD)	Range
Pregnant (>24 weeks)	19	72	(31)	29–173	21	215	(77)	111–398
Non-pregnant	18	74	(27)	42–121	23	109	(48)	47–247
	t_{35} = 0·2088 (NS)				t_{42} = 5·53 ($P < 0{\cdot}001$)			

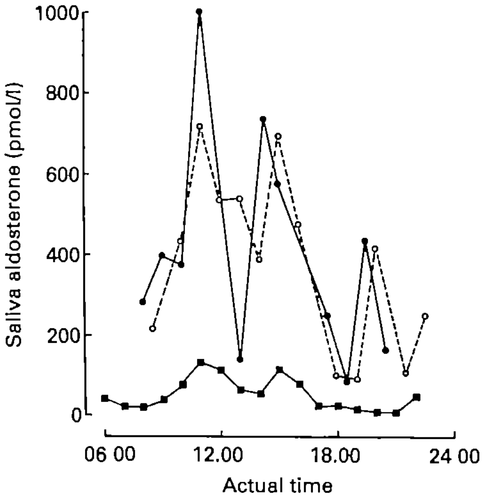

Fig. 1. Diurnal fluctuation in saliva aldosterone before pregnancy (■) and at 26 weeks (○) and 36 weeks (●) gestation.

of the marked variation in saliva aldosterone patterns between subjects, it was not considered appropriate to calculate mean values for all subjects throughout the day. The diurnal variation tended to be similar in each subject from day to day but there were marked differences between subjects so that mean values would be of little significance (Few *et al.* 1987).

Saliva progesterone was measured for only six subject-days; three subjects were at about 26 weeks and three at about 36 weeks. Saliva progesterone was in the range of 1–3 nmol/l and was relatively constant over the period of saliva collection. The mean percentage variation was 14 (SD 4, range 9–12) compared with 51 (SD 18, range 28–71) for aldosterone. Saliva progesterone was not significantly correlated with aldosterone, glucocorticoids or time (Fig. 3).

Figure 4 shows the effect on saliva aldosterone levels of lying in the left lateral position for 105 min on two separate occasions 3 days apart, the subject being a healthy primigravida at 40 weeks. On each occasion the period of lying began at about 14.00 hours. The correlation between log of saliva aldosterone levels and time during the period of lying was highly significant ($r > 0{\cdot}95$). On one day glucocorticoids declined significantly ($P < 0{\cdot}001$) with $t_{\frac{1}{2}} = 151$ min while the subject was lying but on the other day glucocorticoid variation was unrelated to the subject's posture.

Figure 5 shows the diurnal pattern of aldosterone and glucocorticoids in a twin pregnancy complicated by pre-eclampsia at 35 weeks gestation (blood pressure 140/100 mmHg and proteinuria). The patient's saliva aldosterone never exceeded the non-pregnant level (up to 150 pmol/l) at any time during the day; the glucocorticoid profile was also atypical with very low morning levels increasing to a peak in the early afternoon.

In addition to the marked hour-to-hour fluctuation there is also considerable day-to-day variation. Two subjects (nos 2 and 3, Table 1) provided comprehensive series of saliva samples on 2 consecutive days twice during their pregnancy. Table 1 shows considerable difference in the mean aldosterone level between these consecutive days. These between-day differences

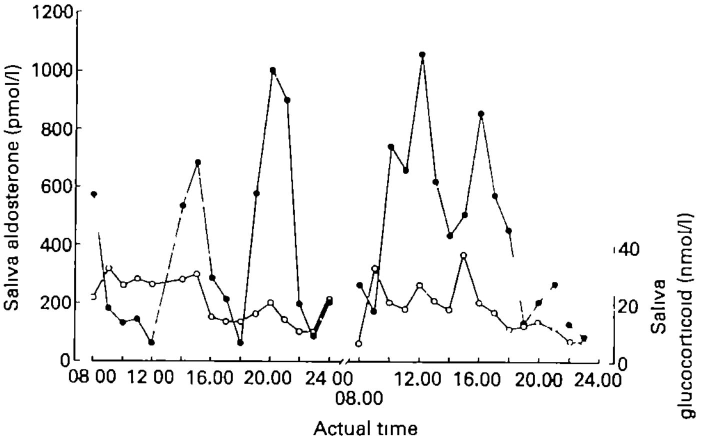

Fig. 2. Comparison of the saliva concentrations of aldosterone (●) and glucocorticoids (○) measured in subject 2 at 28 weeks on 2 consecutive days.

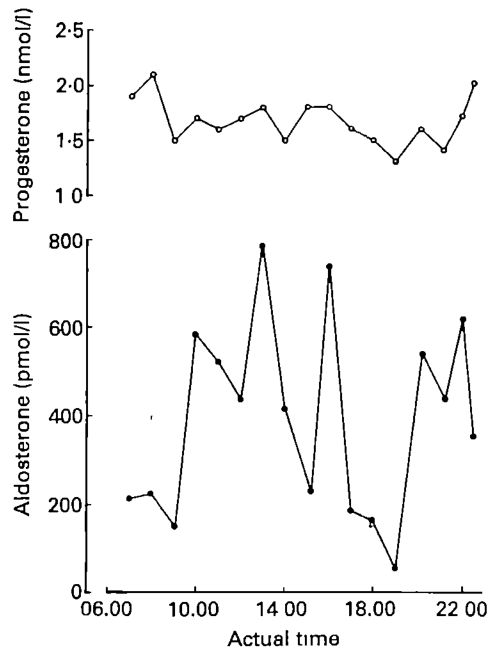

Fig. 3. Comparison of the diurnal patterns of the saliva concentrations of aldosterone (●) and progesterone (○) in a 26-week primigravida. The percentage variations were 48% for aldosterone and 12% for progesterone

can be quantitated by expressing them as a percentage of the mean, and in the four pairs this ranged from 21 to 49% (average 34%) compared with 13–28% (average 18%) for glucocorticoids.

When the mean diurnal saliva aldosterone was calculated using only five samples, collected at approximately 4-h intervals, it was comparable to the corresponding values obtained using all the saliva data available (389, SD 164 pmol/l compared with 383, SD 166 pmol/l, $n = 20$). In 17 of 20 days studied the 4-hourly mean was within 70–130% of the hourly mean.

Discussion

Our data demonstrate that aldosterone concentrations in saliva show considerable diurnal fluctuation during pregnancy. We have shown previously that the concentrations of aldosterone in saliva and plasma are highly correlated (Few *et al.* 1986*a*) so we may infer corresponding changes in plasma aldosterone concentration. Changes in the plasma concentration of any hormone imply changes in the rate of secretion or in the metabolic clearance rate or both. In the case of aldosterone the hepatic plasma flow is an important determinant of the metabolic clearance rate, as the hepatic extraction rate for aldosterone is more than 90%; thus a decrease in hepatic plasma flow leads to a decrease in the metabolic clearance rate. In subjects going about their normal daily activities the hepatic plasma flow will vary in response to changes in posture, physical activity and meals, and will lead to corresponding changes in the metabolic clearance rate. Transition from the supine position to standing results in a decrease in hepatic plasma flow of up to 50% and this probably represents the greatest change that would occur during normal daytime activity. While such a change would lead to an increase in aldosterone concentration, it is difficult to envisage that it could lead to the fluctuations that we have described. We therefore believe that these fluctuations are due to the secretion of aldosterone being intermittent.

The high concentrations of aldosterone in saliva that we have described are thus consistent with the earlier finding that aldosterone secretion is increased threefold during late pregnancy (Jones *et al.* 1959). What is new is the evidence that this enhanced secretion of aldosterone is achieved in a few hours of intense activity by the zona glomerulosa, which otherwise appears to be inactive for much of the day.

Indirect support for this view is provided by the kinetic analysis of the saliva steroid data. This confirms the earlier observation of Tait *et al.* (1962) that the metabolic clearance rate of aldosterone is not different in pregnancy and non-pregnancy. In contrast, the half life of cortisol, whether measured in saliva or plasma

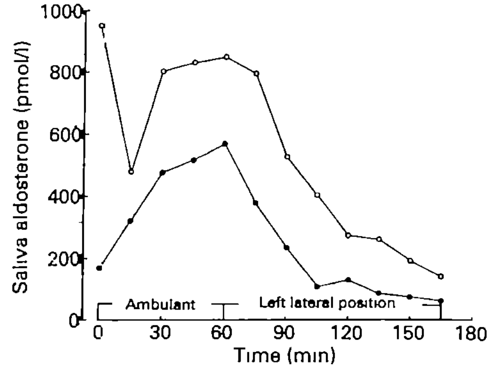

Fig. 4. Effect of lying in left lateral position on saliva aldosterone concentrations on two occasions measured at 40 weeks gestation in a primigravida.

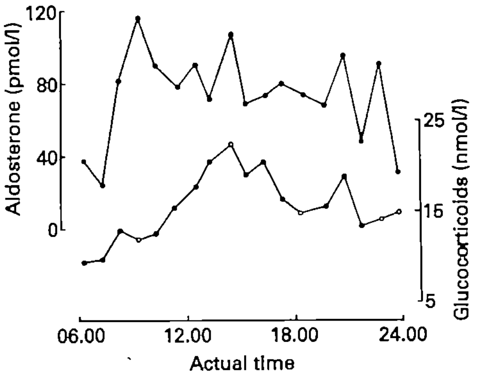

Fig. 5. Diurnal patterns of saliva concentrations of aldosterone (●) and glucocorticoids (○) in a patient with pre-eclampsia.

(Nolten *et al.* 1980; Cousins *et al.* 1986), is considerably extended in pregnancy. The finding that the half life of aldosterone is not altered in pregnancy renders it unlikely that the marked fluctuation in saliva aldosterone is due to some anomaly in the kinetics of aldosterone metabolism.

The recognition that the level of aldosterone fluctuates considerably helps to explain the very wide ranges of plasma aldosterone concentrations that have been reported (Ledoux *et al.* 1975; Dux *et al.* 1984; Few *et al.* 1986*a*) and the poor correlation with plasma renin activity and angiotensin-II concentration (Weir *et al.* 1975). The diurnal pattern of saliva aldosterone in pregnancy shows the same variability that we have found in non-pregnant subjects (Few *et al.* 1987) but in pregnancy the peaks of saliva aldosterone are 5–10 times higher. As in the non-pregnant condition, a common pattern consists of two periods of aldosterone secretion each of 1–2 h resulting in peak levels of saliva aldosterone in the late morning and the afternoon. In one subject (no. 1) from whom we also had saliva samples before pregnancy it is also clear that the effect of pregnancy was essentially to exaggerate the amplitude of the normal aldosterone fluctuation. This suggests that we need not be looking for a more potent stimulus to the zona glomerulosa, but for a mechanism that increases the aldosterone response to normal levels of stimuli. The simplest situation that produces this result is salt deprivation. Change from high to low salt intake (150 down to 20 mmol/day) has no effect upon saliva aldosterone for 20–24 h (Carmichael *et al.* 1986), but within 3 days the mean level doubles and the amplitude of the fluctuation increases (Few *et al.* 1987). In patients with an ileostomy and severe salt loss, peak diurnal saliva aldosterone can exceed that seen in pregnancy and also the level shows profound fluctuation. The precise mechanism of the elevation of aldosterone secretion by salt deprivation has yet to be elucidated, but it is widely believed that increases in the sensitivity of the zona glomerulosa to steroidogenic factors must be involved.

The finding that aldosterone concentration fluctuates more rapidly than the concentration of electrolytes or the plasma volume implies that the aldosterone target organs do not respond to short-term fluctuations in aldosterone concentration but integrate a series of pulses of aldosterone received over a period of hours or even days. The mechanisms which initiate and terminate the periods of aldosterone secretion have yet to be elucidated.

Pregnancy is associated with a decrease in plasma osmolality and sodium concentration (MacDonald & Gould 1971) and it seems reasonable to suggest that this might have a similar effect upon the sensitivity of the zona glomerulosa as salt deprivation. This mild hyponatraemia and reduced osmolality may be regarded as consequences of the elevated progesterone level, as administration of progesterone produces the same effect in men. Progesterone decreases the threshold, and increases the sensitivity of the respiratory centre, leading to hyperventilation and a decrease in $P\text{CO}_2$ which ultimately leads to the sodium and osmolality changes (de Swiet 1980). It thus becomes possible to reconcile the concept that the elevated levels of aldosterone commonly encountered in pregnancy are related to the raised progesterone level with the finding that the concentrations of the two hormones are not statistically correlated. In this respect our finding that saliva progesterone shows little diurnal variation is consistent with recent reports that plasma progesterone concentration shows no circadian variation (Jawad *et al.* 1984; Oestreicher *et al.* 1985). That is, the effect of progesterone is to amplify the normal aldosteronogenic signals, not to stimulate the secretion of aldosterone directly. It should also be noted that both hormones are efficiently cleared from the plasma by the liver, so any factors that affect liver blood flow (such as postural change or meals) will have parallel effects on both hormones due to alterations in the metabolic clearance rates.

The degree of fluctuation in aldosterone levels implies that single determinations of this hormone, in either saliva or plasma, are of limited value in patient care or research. Many investigators seem to be aware of a potential problem in measuring aldosterone in pregnant women when they state that the subject was kept in the left lateral position for some arbitrary time before blood was drawn for aldosterone determination, presumably on the assumption that this brings the subjects into a basal or equilibrium state. However, it can be seen from Fig. 4 that the saliva aldosterone level only stabilizes when it has declined to essentially non-pregnant levels. This implies that if the aldosterone concentrations of samples (plasma or saliva) are substantially above non-pregnancy levels then the samples will have been collected when the aldosterone level was declining exponentially. Thus the basal level of aldosterone during pregnancy is probably quite low but upon this are superimposed periods of intense aldosterone secretion resulting in the well-known high concentrations.

What is needed to assess aldosterone status during pregnancy is a method of integrating the fluctuating concentration over the whole day. In principle, measurement of urinary aldosterone should fulfill this role but there are still difficulties with the measurement of aldosterone in urine, and collection of urine is inconvenient to the subjects. We have shown previously (Few *et al.* 1987) that aldosterone measured at 4-h intervals in saliva provides a useful estimate of the mean diurnal level of aldosterone, and our present data extend this finding to the pregnant condition.

It has been reported by several groups of investigators (e.g. Weir *et al.* 1973; Pedersen *et al.* 1982) that plasma aldosterone concentration is low in pre-eclampsia. When we first appreciated the degree of diurnal fluctuation of saliva aldosterone we suspected that these findings in pre-eclampsia might be an artefact due to inappropriate time of sampling. However, it is clear from the data obtained in one pre-eclamptic patient (blood pressure 140/100 mmHg and proteinuria) that this view was incorrect, and that, at least in this patient, aldosterone secretion does not rise above the non-pregnant level at any time of the day. It is unlikely that this finding can be merely attributed to bed-rest. In 18 normal pregnancies the early morning mean saliva aldosterone, following overnight recumbency, was 435 pmol/l (SD 245, range 125–1048). While the aetiology of pre-eclampsia is still controversial it is premature to speculate on the significance of the paradoxically low aldosterone level in association with raised blood pressure. Nevertheless, measurement of aldosterone levels in saliva offers a convenient method of investigating this anomaly.

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Leukotrienes in human umbilical plasma at birth

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Summary. The aim of this study was to see whether leukotrienes are present in human umbilical plasma at birth either before or after labour. Plasma concentrations of LTB_4 (6·02 ng/ml) and LTD_4 (6·11 ng/ml) were significantly higher ($P<0{\cdot}01$) after spontaneous vaginal delivery than during elective caesarean section before labour (LTB_4 = 1·96 ng/ml, LTD_4 = 0·18 ng/ml). A possible involvement of leukotrienes in the biochemical and metabolic events of human labour is suggested.

After an appropriate stimulus, cells of animal tissues respond with the activation of a phospholipase which cleaves the fatty acid precursor, such as arachidonic acid, from the phospholipids that constitute the lipid bilayer of the cell membrane. Free arachidonic acid can activate several enzyme systems including the cycloxygenase pathway which converts it into thromboxane and prostaglandins (including prostacyclin PGI_2) through the formation of unstable intermediate endoperoxides, and the lipoxygenase pathway (another group of enzymes) which catalyses the formation of the HPETE compounds successively transformed in leukotrienes (LT).

The involvement of cycloxygenase metabolites, particularly PGE_2 and $PGF_{2\alpha}$, in the biochemical events of human parturition is well documented (Lackritz *et al.* 1978; Okazaki *et al.* 1981*a*; Karim & Devlin 1967; Keirse 1979). However, information on the role played by lipoxygenase metabolites is lacking.

Amniotic concentrations of LTB_4, 12-HETE and 15-HETE increase during labour, which suggests an increased activity in the uterus of the group of enzymes collectively referred to as lipoxygenases (Mitchell 1986). That observation may be of great significance since arachidonate lipoxygenase products, particularly leukotrienes, display some powerful biological activities (Sirois 1985). The eventual involvement of these products in the biochemistry of human labour seemed worth further study. The present investigation was undertaken to see whether or not the concentration of leukotrienes in human umbilical plasma in infants born by elective caesarean section before labour would differ from concentrations in infants born after labour.

Patients and methods

The study included 14 normal pregnant women at term; seven of them had a spontaneous vaginal delivery without having any kind of drug during labour and they formed the first group; the other seven were delivered by elective repeat caesarean section before labour, they formed the second group.

Gestational age, calculated on the basis of the last menstrual period and confirmed by ultrasound examination, was comparable between the two groups. Birthweights and Apgar scores were also comparable.

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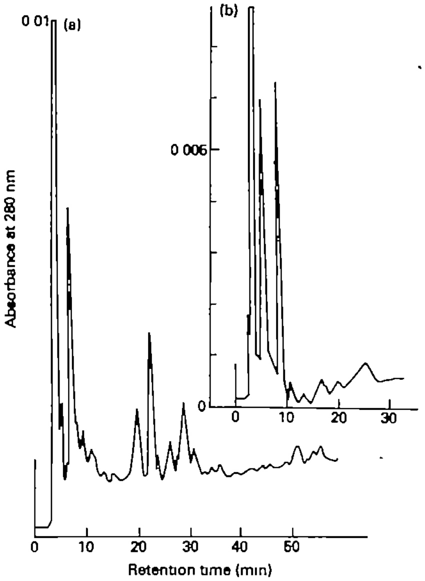

Fig. 1. High-performance liquid chromatographic analysis of lipoxygenase metabolites. The extracts were resuspended in methanol and injected in a Lichrosorb RP-18 column (5 µm particle size). Elution was obtained at a flow of 1 ml/min using the solvent water: methanol (67:33 v/v) pH 4·0. Retention times were 24 min for LTB$_4$ and 29 min for LTD$_4$. Absorbance was determined at 280 nm. The attenuation setting of u v. spectrophotometric detector was 0·01 AUFS. Chromatogram of an umbilical plasma sample taken (a) at vaginal delivery and (b) during caesarean section before labour.

Sample collection

Mixed artery and vein blood (10 ml), taken from umbilical vessels immediately after birth of the fetus, was collected in tubes containing EDTA as anticoagulant, and mixed with an equal volume of ice-cold solution containing serine/borate 10 mM in saline.

After centrifugation at 3000 r/min for 15 min at 4°C the samples were processed for chromatographic analysis.

Analysis of lipoxygenase metabolites

A slight modification has been developed to the chromatographic method described by Powell (1982) to extract leukotrienes from biological fluids using the octadecylsilyl silica reversed-phase (SEP PAK cartridges, Water Associates, Milford, MA, USA). Cartridges were prewashed with absolute ethanol (20 ml), water (20 ml) and 0·1% EDTA solution (5 ml). Briefly, each sample of plasma was applied directly to the SEP PAK cartridge after acidification (pH 4·0). The cartridge was then washed with distilled water (20 ml), aqueous ethanol (15% v/v) and water. To remove any prostaglandins and thromboxane, the cartridge was washed with methyl formate before elution of the leukotrienes with ethyl acetate and methanol. Ethyl acetate and methanolic fractions were then evaporated to dryness at 30°C under vacuum in a Buchi Rotavapor RE 121. Analytical reversed-phase high-performance liquid chromatography (HPLC) was used for the final purification and identification of leukotrienes. Because of the high absorbance of the conjugated triene, the detection of leukotrienes is very sensitive at 280 nm. Dried fractions were resuspended in methanol (100 µl), filtered, and the clear solution was applied to a Lichrosorb RP-18 column (5 µm particle size) (LKB), with methanol:water (67:33) pH adjusted to 4·0 with acetic acid as the mobile phase.

LTD$_4$ and LTB$_4$ were identified by ultraviolet (u.v.) spectra and absorbance ratio during the run with a spectrophotometric detector LC-85B (Perkin Elmer); LTB$_4$ has a u.v. maximum of 270 nm ($\varepsilon = 51\,000$) with peaks at 260 nm and 281 nm, and LTD$_4$ has a u.v. maximum of 280 nm ($\varepsilon = 40\,000$) with peaks at 270 nm and 292 nm (Murphy & Mathews 1982).

Retention times were calculated by coelution with the standards. (LTB$_4$ and LTD$_4$ were a kind gift from Wellcome Italia.)

LTD$_4$ and LTB$_4$ were estimated by comparing the areas of the respective peaks with that of standards. The peak areas or heights were calculated using a LCI 100 Laboratory Computing Integrator (Perkin Elmer).

Standards curves of the individual leukotrienes were obtained with five different concentrations (1·5625–25 ng) and showed the following correlations: LTB$_4$ $r = 0{\cdot}978$, LTD$_4$ $r = 0{\cdot}989$. The minimum detectable quantities were 1·5 ng for LTD$_4$ and 1·0 ng for LTB$_4$.

In order to check further the quantitative reliability of peaks identified as LTB$_4$ and LTD$_4$, acetate and methanolic fractions were analysed by a System Diode Array Detector LC 235 Model (Perkin Elmer). This analytical procedure allowed us to obtain the following data: (1) wavelength changes; (2) absorbance maxima; (3) purity indexes; (4) chromatogram as absorbance profile map, at wavelength from 195

Table 1. LTD_4 concentrations in human umbilical plasma after vaginal delivery and during elective section

Vaginal delivery		Elective caesarean section	
Patient	LTD_4 (ng/ml)	Patient	LTD_4 (ng/ml)
1	6·25	8	ND
2	6·69	9	1·25
3	6·20	10	ND
4	6·50	11	ND
5	6·20	12	ND
6	4·25	13	ND
7	6·70	14	ND
Mean (SD)	6·11 (0·84)*	Mean (SD)	0·18 (0·46)

ND, Non-detectable. *Significance of difference between the two groups $P<0·01$.

Table 2. LTB_4 concentrations in human umbilical plasma after vaginal delivery and during elective section

Vaginal delivery		Elective caesarean section	
Patient	LTB_4 (ng/ml)	Patient	LTB_4 (ng/ml)
1	7·80	8	2·40
2	8·20	9	ND
3	ND	10	4·12
4	7·50	11	ND
5	5·20	12	2·50
6	6·25	13	2·70
7	7·22	14	1·70
Mean (SD)	6·02 (2·84)*	Mean (SD)	1·96 (1·51)

ND, Non-detectable. *Significance of difference between the two groups $P<0·01$.

nm to 370 nm. (These analytical data have been submitted to *Journal of Chromatography.*)

Recoveries of LTB_4 and LTD_4 were calculated by adding a known amount to 1 ml of phosphate-buffered saline (pH 7·4). These samples were processed as above. Final recovery averaged 50% for LTD_4 and 75% for LTB_4. The overall recovery was obtained by adding the respective leukotriene to cord plasma obtained at caesarean section (37°C) and immediately followed by the extraction procedure to avoid a possible plasma conversion.

Comparing chromatograms of these samples with those of the same samples without added standards (blank), we observed no overlapping peaks for LTD_4, and for LTB_4 the natural occurring amount was about 4·2%. Final recovery of leukotrienes from cord plasma averaged 72 (SD 6·8)% for LTB_4 and 66 (SD 5·2)% for LTD_4.

Fisher's test was used for the statistical calculations.

Results

The comparative analysis by HPLC of plasma from the umbilical blood of the two groups under investigation revealed the presence of markedly different quantitative chromatographic patterns (Fig. 1).

LTD_4 was present in the umbilical plasma samples of the vaginal delivery group at a mean concentration of 6·11 ng/ml (SD 0·84); only in one sample was the concentration outside the range 6·20–6·70 ng/ml (4·25 ng/ml). On the other hand, LTD_4 was not detectable in the umbilical plasma samples of the caesarean section group, with the exception of one sample showing a concentration of 1·25 ng/ml (Table 1).

There was more variability in the concentration of LTB_4 in all samples of umbilical plasma of the vaginal delivery group (mean 6·02, SD 2·84 ng/ml). But except for one sample where LTB_4 was undetectable the levels were all higher than in the samples from the section group (mean 1·96, SD 1·51 ng/ml) (Table 2).

Discussion

These data demonstrate that both LTD_4 and LTB_4 are present in umbilical plasma of infants born after physiological labour; on the other hand LTB_4 and LTD_4 are not detectable in 2 of 7 and 6 of 7, respectively, umbilical plasma samples from infants born by elective section before labour. It is to be noted that high levels of leukotrienes are found in umbilical cord plasma of infants born after spontaneous labour and vaginal delivery. Mitchell (1986) has described umbilical prostaglandin levels in labour ranging around 200 pg/ml. But it has been reported that levels of leukotrienes of 18 ng/ml can be measured in human whole blood after stimulation with calcium ionophore A 23187 (Patrignani & Canete Soler 1987), so that activation of the lipoxygenase pathway might take place during labour with a consequent rise in the level of these metabolites in the blood. To hypothesize a physiological role of leukotrienes in the biochemical events culminating in labour therefore seems reasonable.

Certainly their origin remains to be investigated, are they from fetal or maternal tissues or both? It should be recalled that human amniotic membranes after vaginal delivery convert more arachidonic acid into monohydroxytetraenoic C_{20} fatty acids than in the absence of labour (Kinoshita *et al.* 1980).

Arachidonate lipoxygenase metabolites, particularly leukotrienes, could be involved in some biochemical events of labour because of their involvement in contractions. LTD_4 has been shown to stimulate uterine contractions (Carraher *et al.* 1983; Weichman & Tucker 1982) and could play a role in the regulation of myometrial contractions during labour.

Furthermore, LTB_4 is a calcium ionophore (Serhan *et al.* 1982), and its production by intrauterine tissues in labour could stimulate the calcium-dependent phospholipases (Okazaki *et al.* 1981*b*) to release more free arachidonic acid available for eicosaenoid synthesis But extensive work is needed to discover both the sources of leukotrienes in the fetal circulation at birth and their role in the biochemistry of labour.

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Cigarette smoking in pregnancy results in marked decrease in maternal hCG and oestradiol levels

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Summary. We have examined serum levels of oestradiol (E_2), sex-hormone binding globulin (SHBG) and human chorionic gonadotrophin (hCG) during early pregnancy in relation to smoking status at the time of sampling in a series of 147 women. Smoking was associated with significantly depressed serum levels of E_2, SHBG and hCG: in smokers, E_2 levels were on average 17·6% lower (P=0·037), SHBG levels were 12·4% lower (P=0·15), and hCG levels were 21·5% lower (P=0·044). There appeared to be a steady decline in these values with increasing cigarette consumption. These lower hormone levels in smokers may explain certain adverse effects of smoking in pregnancy.

A number of epidemiological studies of testicular cancer have found an increased risk associated with maternal exposure to exogenous oestrogens during the index pregnancy (Henderson *et al.* 1979; Schottenfeld *et al.* 1980; Depue *et al.* 1983; Moss *et al.* 1986). We have previously proposed that elevated maternal endogenous oestrogen levels in the index pregnancy also may increase the risk of cancer of the testis (Depue *et al.* 1983): this was suggested by the finding that high maternal body-weight before conception (Depue *et al.* 1983) and extreme nausea during the index pregnancy (Henderson *et al.* 1979; Depue *et al.* 1983; Brown *et al.* 1986) also may be risk factors for cancer of the testis, since both these factors are associated with higher 'effective' endogenous oestrogen levels. There is a strong inverse relation between sex-hormone binding globulin (SHBG) levels and body-weight (Nisker *et al.* 1980), so that body-weight is positively associated with bioavailable (non-SHBG bound, and 'free') oestradiol (E_2) (Siiteri *et al.* 1981). Women experiencing extreme nausea and vomiting during pregnancy have significantly raised first trimester E_2 levels (Depue *et al.* 1987).

Other factors that may affect maternal oestrogen levels are of great interest, not only in their own right, but because they may provide further insight into the precise role of maternal hormones in the aetiology of testicular cancer. The recent results of McMahon *et al.* (1982) and Michnovicz *et al.* (1986) suggest that smoking may be such a factor. These investigators found in non-pregnant, menstruating women that urinary oestrogen (oestrone (E_1), E_2 and oestriol (E_3)) levels are significantly lower in smokers than in non-smokers. McMahon *et al.* (1982) suggested that this was caused by a direct effect

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of smoking on the ovary, while Michnovicz *et al.* (1986) showed that the breakdown pathways of E_2 were significantly affected by smoking, and specifically that the extent of 2-hydroxylation of E_2 is significantly increased among smokers.

In this report we have examined serum levels of E_2, SHBG and human chorionic gonadotrophin (hCG) during early pregnancy in relation to smoking status at the time of sampling in a series of 147 women who participated in a multicentre study in the early 1960s.

Subjects and methods

The study subjects were participants in the Collaborative Perinatal Project (CPP) of the National Institute of Neurological and Communicative Disorders and Stroke (Bethesda, MD, USA), a prospective study conducted to identify aetiological factors related to adverse pregnancy outcome (Niswander & Gordon 1972). In the CPP, more than 55 000 pregnancies were registered at 12 university-affiliated medical centres in the USA between 1958 and 1965. Most of these pregnancies were beyond 20 weeks (measured from day 1 of the last menstrual period (LMP)) at the time of registration. Blood samples were collected at each prenatal visit and stored in Bethesda, MD, USA, at −20°C. A detailed medical history was obtained from each participant and detailed obstetric and delivery records were kept.

We have used these blood samples for several studies of maternal hormone levels during the first trimester of pregnancy. To examine the effects of smoking on these hormone levels, we have combined the results from four of these studies: (1) the first pregnancy of 33 white women who were included in our study comparing a woman's first with her second pregnancy (Bernstein *et al.* 1986) (Study A); (2) 34 white control women in our case-control study of hyperemesis gravidarum (Depue *et al.* 1987) (Study B); (3) 36 white women in their first pregnancy in a study designed to compare pregnancy hormone levels across ethnic groups (Study C: Henderson *et al.* (1988) present results for 20 of these women); and (4) 44 white women selected as controls for a case-control study of cryptorchidism (Study D: results not previously published). Because of the design of these studies, most of these women were primigravid at the time of sampling. Mean values for age, pre-pregnancy body-weight (weight at time of sampling is not known), parity, length of gestation (days since first day of LMP) and smoking status at the time of sampling are shown in Table 1 for each of these studies. None of the women suffered from hyperemesis or pre-eclampsia during the pregnancy, each pregnancy was full term, and each offspring was followed for 7 years, with no malformations being noted.

All E_2 assays were conducted in the laboratory of Howard L. Judd, MD (University of California, Los Angeles) using the method of Devane *et al.* (1975). SHBG-binding capacity (SHBG-bc) was measured at the Endocrine Sciences Laboratory (Tarzana, California) in the samples from studies A, B and C by the selective ammonium sulphate precipitation technique

Table 1. Comparison of characteristics of women from the individual studies included in the analysis of smoking effects on early pregnancy hormone levels

Characteristic	Study A	 B	 C	 D
Sample size (*n*)	33	34	36	44
Nulliparous (*n*)	33	15	36	19
Age (years)*	22·6 (3·2)	23·0 (3·8)	22·7 (3·3)	25·7 (5·2)
Pre-pregnancy body-weight (kg)*	56·9 (7·9)	55·7 (8·0)	52·7 (7·4)	58·3 (11 4)
Length of gestation (days)*	84·1 (15·7)	70·5 (17·3)	66·8 (10·4)	73·8 (11·1)
Smoking status at time of sampling				
Non-smokers	51·5%	52·9%	55·6%	63·6%
Cigarettes/day				
1–5	9·1%	8·8%	11·1%	13·6%
6–10	12·1%	14·7%	19·4%	6·8%
11+	27·3%	23·5%	13·9%	15·9%

* Mean values (SD) shown.

described by Nankin *et al.* (1975) using a tritiated dihydrotestosterone reference. hCG was measured by radioimmunoassay (Vaitukaitis *et al.* 1972) at the Endocrine Sciences Laboratory in the samples from studies B, C and D. All samples for a given study were assayed as a group. As samples were collected over a 6-year period, we examined plots of hormone values by the date of sample collection and found no evidence of degradation with increasing storage time.

For statistical analysis, hormone and SHBG-bc levels were transformed to logarithmic values to achieve approximate normality of distributions, and geometric mean levels are presented in the Tables. The relations of hormone and SHBG-bc levels to length of gestation and to pre-pregnancy body-weight were assessed by standard regression techniques and were found not to differ significantly from linear over the range of gestational times studied. Analysis of covariance techniques (Kleinbaum & Kupper 1978) were therefore used to test for differences in hormone and SHBG-bc levels by smoking status. All statistical significance levels (*P*-values) quoted are two-sided. Because hormone and SHBG-bc levels were determined at separate times for each study, we adjusted for study (data set) in all the analyses.

Results

The characteristics of all of the women by smoking status at time of blood sampling are given in Table 2. Smokers and non-smokers were similar in terms of age, pre-pregnancy body-weight and length of gestation at the time of sampling. For the subgroups for whom we have SHBG-bc and hCG assay results, smokers and non-smokers were equally comparable on these characteristics (results not shown).

Table 2. Characteristics of subjects

Variable	Smoking status at sampling	
	Non-smoker	Smoker
Sample size (*n*)	83	64
Age (years)*	23·4 (3·9)	24·0 (4·7)
Pre-pregnancy body-weight (kg)*	56 (10)	56 (8·2)
Length of gestation (days)*	74·6 (16·2)	73·4 (13·1)

*Mean values (SD) shown.

The geometric mean levels of E_2 (adjusted for length of gestation) of smoking women were, on average, 17·6% lower than those of non-smoking women (P=0·037; Table 3) When the women were stratified according to pre-pregnancy body-weight, smokers had lower E_2 levels in all weight categories (results not shown), but adjusting the comparison between smokers and non-smokers for pre-pregnancy body-weight did not affect the results presented. The results are compatible with a steady decline in E_2 levels with increasing cigarette consumption.

Smokers had SHBG-bc levels (adjusted for length of gestation) that were, on average, 12·4% lower than those of non-smokers (P=0·15, Table 3). SHBG-bc levels declined with pre-pregnancy body-weight, but adjusting the comparison between smokers and non-smokers for pre-pregnancy body-weight did not affect the results presented (the 12·4% lower value in smokers became 12·0%). The results are compatible with a steady decline in SHBG-bc levels with increasing cigarette consumption. When, in addition to adjusting for length of gestation and pre-pregnancy body-weight, adjustment of the SHBG-bc results was made for the associated E_2 concentrations, this accounted for most of the difference observed between smokers and non-smokers; with this adjustment, smokers had a mean SHBG-bc level that was only 4·3% lower than that of non-smokers. Adjustment of the E_2 values for the associated SHBG-bc values did not account for the difference in E_2 values between smokers and non-smokers—the observed difference was reduced by 23%.

After adjusting for length of gestation, mean hCG levels were 21·5% lower in smokers than in non-smokers (P=0·044; Table 3). Adjustment for pre-pregnancy body-weight did not alter the observed smoking effects. There appears to be a steady decline in hCG with increasing cigarette consumption. Adjusting the hCG values for the associated E_2 values did not account for the difference in hCG values between smokers and non-smokers—the observed 21·5% difference was only reduced to 16·6%. In contrast, adjusting the E_2 values for the associated hCG values accounted almost completely for the difference in E_2 values between smokers and non-smokers—the observed difference was reduced by 70%.

Table 3. Adjusted geometric mean oestradiol (E_2), sex-hormone binding globulin-binding capacity (SHBG-bc) and human chorionic gonadotrophin (hCG) levels in sera by smoking status at time of sampling

Variable	Smoking status at sampling				
	Non-smoker		Smoker		*P*-value*
Sample size (*n*) for E_2	83		64		
E_2 (pg/ml)†	158·7		130·7		0·037
By cigarettes per day	None	1–5	6–10	11+	
n	83	16	19	29	
	158·7	152·5	125·5	123·5	0·025**
Sample size (*n*) for SHBG-bc	55		48		
SHBG-bc (μg/dl)†	5·93		5·20		0·153
By cigarettes per day	None	1–5	6–10	11+	
n	55	9	16	23	
	5·93	5·87	4·91	5·17	0·182**
Sample size (*n*) for hCG	66		48		
hCG (i.u./ml)†	50·5		39·6		0·044
By cigarettes per day	None	1–5	6–10	11+	
n	66	13	15	20	
	50·5	47·3	40·9	34·4	0·013**

†All geometric means adjusted for data set and length of gestation.

**P*-value associated with analysis of covariance *F*-test, with adjustment for data set and length of gestation.

***P*-value for trend with adjustment for data set and length of gestation

Discussion

The results shown in Table 3 indicate that there is a pronounced depression of serum levels of E_2, SHBG-bc and hCG in smokers, and that the effects are directly related to the number of cigarettes smoked per day. The decreased levels of E_2, SHBG-bc and hCG in smokers were evident over the whole range of lengths of gestation studied, i.e. 43–113 days (6–15 weeks) since LMP. The smoking effect on E_2 is largely explained in statistical terms by the associated hCG effect. The hCG result suggests that the main effect of smoking is a direct one on the placenta, and that between-person differences in level of E_2 mirror differences in their hCG levels, i.e. the level is probably a direct measure of general placental function. Although there may be a direct effect of smoking on serum E_2 levels along the lines suggested by Michnovicz *et al.* (1986) this appears to be at most only a minor determinant of the smoking effect on serum E_2. The E_2 level then appears to determine the level of SHBG-bc. We did not measure non-protein-bound or SHBG-bound E_2 and do not know whether smoking alters the level of bioavailable E_2.

These results suggest that early progesterone levels are also likely to be depressed in smokers. We have at present no data on this. Data on 17-OH-progesterone levels in early pregnancy should show whether ovarian steroid production is affected by smoking.

Smoking in pregnancy is associated with a number of adverse effects (Barron & Thomson 1983). Decreased hormone levels must now be added to the list of possible mechanisms of these harmful effects. In particular, it is known that miscarriage can be caused by certain alterations in hormone levels and it may be that this is how smoking increases this particular risk.

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Problems of peritoneal access in intraperitoneal treatment and monitoring of ovarian cancer

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Summary. A total of 154 peritoneal lavages was attempted through either a permanent (17) or a temporary percutaneous cannula (137) in 59 ovarian cancer patients undergoing intraperitoneal treatment or monitoring. Seven of the eight permanent catheters were removed because of complications; intraperitoneal adhesions were a major problem in this group. Overall, 137 temporary catheters were inserted (14G Venflon i.v. cannula in 119, Verres needle in 15, and a Trocath peritoneal dialysis catheter in 3 instances) but it was not possible to perform a peritoneal lavage in 42 (30%). Access to the peritoneal cavity was unsatisfactory on 29 (34%) occasions when a Venflon cannula was used, either because there was inadequate flow of lavage fluid into the peritoneal cavity or this was limited by pain. Perforation of the bowel occurred in 12 (9%) cases but there was no significant morbidity. Problems with achieving reliable peritoneal access using either permanent or temporary catheters may limit the potential advantages of the intraperitoneal route for treatment and monitoring.

Epithelial ovarian cancer has a worse prognosis than any other gynaecological cancer, causing more deaths per year than cervical and uterine cancer combined (OPCS 1985, 1986). These facts emphasize the importance of developing and assessing new approaches to the management of this disease.

Epithelial ovarian cancer is largely confined to the peritoneal cavity which has important implications for both treatment and monitoring. Intraperitoneal therapy can deliver chemotherapy in high concentrations to the tumour, potentially with less systemic toxicity, thereby enhancing the therapeutic index. It is necessary to deliver the treatment in a sufficient volume of fluid to ensure uniform peritoneal distribution (Dunnick *et al.* 1979). This fluid may also furnish cytological and tumour marker information on patients who may not be assessable otherwise (Redman *et al* 1987)

The theoretical advantages of intraperitoneal treatment and monitoring depend on adequate access to the peritoneal cavity such that 1–2 litres of peritoneal lavage fluid can be repeatedly and reliably delivered. The two main options, either a permanent indwelling catheter or a temporary single-use catheter or cannula, both have their advocates (Tenckhoff & Schechter 1968; Piccart *et al.* 1985; Runowicz *et al.* 1986) but the published experience to date is limited and conflicting We have reviewed our experience of gaining peritoneal access using indwelling and tempo-

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rary catheters for monitoring and treating ovarian cancer.

Patients and methods

This study included 59 patients with epithelial ovarian cancer in whom peritoneal access for intraperitoneal treatment or monitoring was required, using either an indwelling catheter or a temporary, single-use cannula. Their charcteristics are summarized in Table 1. Treatment was the main indication for peritoneal access in patients with an indwelling catheter. Intraperitoneal chemotherapy was usually given as a second-line treatment to patients with small volume residual disease after a debulking laparotomy, so that most patients had had more than one laparotomy. The majority of peritoneal lavages via temporary cannulae were for monitoring purposes, performed in a heterogeneous group of patients with ovarian cancer.

Permanent indwelling catheters were inserted under direct vision at laparotomy, using either a Tenckhoff (Lifemed, Compton, California, USA) or a Life-Coil (Shuco, London, UK) catheter. To ensure patency the catheters were flushed with 1000 ml dextran over 24 h, then daily for 7 days with 5 ml heparinized saline (3000 U heparin) and thereafter three times a week. Upon completing therapy the catheters were removed under direct vision at laparotomy, which was done primarily to assess response but also to assess the intraperitoneal reaction to the catheter.

Table 1. Characteristics of 59 patients in permanent and temporary catheter groups*

	Permanent (n = 8)	Temporary (n = 55)
Age (years)		
median (range)	54 (45–66)	56 (38–84)
Residual disease (cm)†		
0	1	12
<2	6	11
>2	1	32
FIGO stage		
I	0	5
II	1	4
III	6	40
IV	1	6
No. of previous laparotomies‡		
0	0	1
1	1	47
2	5	7
3	2	0

* Four patients who had both catheters are included in both groups.

† χ^2 = 11·149, d f. = 2, P<0·01.

‡ χ^2 = 28·377, d f. = 2, P<0·001

Three types of temporary catheter were used: a 14G 45-mm Venflon i.v. cannula (Viggo, Helfingborg, Sweden), a 14G 70-mm Verres insufflation needle, or a Trocath peritoneal dialysis catheter (Kendall McGaw, Sabana Grande, Puerto Rico). The cannulae were inserted percutaneously into the peritoneal cavity after infiltration of the skin and subcutaneous tissue with 0·5% lignocaine. Following insertion, the plunger of a syringe containing 0·9% saline and attached to the cannula was drawn back to ensure that the bowel had not been entered. Correct placement was confirmed if an adequate flow of saline was possible. If not, the catheter was removed and a further final attempt was made. At the end of the procedure the catheter was removed.

For diagnostic or monitoring peritoneal lavage, 1 litre of warmed 0·9% saline was infused under gravity into the peritoneal cavity, and after 5 min a 20-ml sample was taken for cytological and other studies. Peritoneal lavage performed solely for monitoring purposes was an outpatient procedure After the sample was obtained, the remaining saline was left to be absorbed. When performed in conjunction with intraperitoneal chemotherapy, an additional litre of 0·9% saline was infused before the instillation of therapy which usually comprised cisplatinum and mitoxantrone. After 4 h the peritoneal cavity was drained as far as possible.

Results

A total of 154 peritoneal lavages was attempted in 59 patients (median number procedures per patient 2, range 1–7). The principal indications for peritoneal access for each catheter type are shown in Table 2. In four patients, both indwelling and temporary catheters were used; temporary catheters were used after the failure of the indwelling catheter in three patients, and one patient received intraperitoneal therapy via an indwelling catheter after a positive diagnostic lavage performed via a temporary cannula.

Table 2. Peritoneal lavage procedures—primary indication and type of peritoneal catheter (no. of patients in parentheses)

Indication	No. of procedures with Permanent catheter	Temporary catheter	Total
Treatment	16 (7)*	9 (6)*	25 (10)*
Monitoring	1 (1)†	128 (49)†	129 (49)†
Total	17 (8)	137 (55)	154 (59)

* Three patients had both permanent and temporary catheters.

† One patient had both permanent and temporary catheters.

Indwelling catheters

Eight indwelling catheters were inserted, although seven were eventually removed because of complications (Table 3). In two women peritoneal access was never possible because of a vaginal vault fistula caused by the catheter tip in one, and post-surgical peritonitis due to the breakdown of an entero-colonic anastomosis in the other, although the catheter was not implicated. The remaining five catheters were removed either because the catheter was blocked or the flow slow and painful as a result of dense intraperitoneal adhesions (associated with progressive disease in two patients).

Seventeen lavages were performed in six patients. On 12 occasions the requisite volume of lavage fluid was administered, although this was painful, and required narcotic analgesia in five instances. It was not possible to drain the peritoneal cavity after intraperitoneal treatment on four occasions.

Temporary catheters

A total of 137 temporary catheters was inserted, 134 procedures were performed by one author (C.W.E.R.). Satisfactory peritoneal access was not achieved in 42 (30%) for the reasons listed in Table 4. The bowel may have been perforated on 12 (8·6%) occasions as bowel contents or gas were noted on drawing back on the syringe plunger after insertion on five occasions, and seven patients developed mild colicky abdominal pain following the administration of the lavage fluid. There were no significant sequelae other than a transient pyrexia in one patient and a mild puncture site infection in another that required no treatment. In 29 instances when the relatively short 45-mm Venflon was used, the procedure was abandoned either because the flow of fluid was unsatisfactory or there was associated discomfort, usually due to fluid going into the subcutaneous or subfascial layers in the anterior abdominal wall. On one occasion a superficial blood vessel was punctured but haemostasis was easily achieved using local pressure with no resultant haematoma.

Peritoneal access was required for intraperitoneal therapy in 10 patients, using either an indwelling (7) or a temporary catheter (3). The intention at the onset of treatment was to give up to five treatment cycles; 23 cycles (median 2, range 0–5) were administered. Intraperitoneal treatment was discontinued prematurely in nine patients; in three because of disease progression, in two because of toxicity, and in four patients because of problems with peritoneal access.

Discussion

A permanent catheter avoids the hazards of repeated puncture of the abdominal wall and peritoneum but this advantage must be offset against the problems of leaving a catheter *in situ*, which include peritonitis, catheter blockage, pain, leakage, dislodgement and exit site infections (Ozols *et al.* 1984; Speyer *et al.* 1980; Bast *et al.* 1983; Jenkins *et al.* 1982) It has been reported that in ovarian cancer patients up to 67% of permanent catheters develop complications (Runowicz *et al.* 1986). Our experience indicates that in ovarian cancer prolonged use of indwelling catheters is usually not possible due to the development of dense intraperitoneal adhesions. However, the use of an implanted

Table 3. Outcome in patients with permanent catheters

No. of catheters inserted	8
Complications necessitating removal	
Fistula	1
Peritonitis	1
Adhesions	4
Blocked catheter	1
No procedures	17
Successful	12
Pain	5
Failure to drain	4
Failed	5

Table 4. Outcome in patients with temporary catheters (% of total in parentheses)

	Venflon	Verres	PD catheter	Total
No. of procedures	119	15	3	137
Failed access				
Perforated bowel	11	1	0	12 (9)
Pain	11	0	0	11 (8)
No flow	18	0	0	18 (13)
Haemorrhage	1	0	0	1 (1)
Total	41	1	0	42 (30)
Complications				
Puncture site sepsis	1	0	0	1
Transient pyrexia	1	0	0	1
Failure to drain	6	0	0	1
Total	8	0	0	8 (6)

subcutaneous portal to reduce the likelihood of infection, and further attention to the optimal siting and intra-abdominal length of indwelling catheters may improve and prolong access.

The main objection to temporary catheters is the risks associated with their placement, especially in ovarian cancer patients. However, Runowicz *et al.* (1986) reported no failed attempts in 105 temporary catheter placements in 21 patients, though three developed inflammatory pelvic masses requiring a laparotomy, and the bladder was entered on one occasion (a complication rate of 3·8%). There were far fewer complications using temporary catheters than with the Tenckhoff catheter. All the patients in that series had minimal residual disease and had been selected for repeated peritoneal access. In our series, 30% of catheter placements were unsuccessful although there were no significant complications. The higher failure rate in our series is largely attributed to the use of an intravenous cannula that was too short, so that the peritoneal cavity was not entered on 29 occasions accounting for 69% of the failed attempts. This problem was reduced by the use of a longer Verres insufflation needle. In addition the spring-loaded obturator of the Verres needle should reduce the likelihood of bowel perforation. In all, the bowel was perforated on 12 occasions (9% of all attempts), and on one occasion this was associated with the use of a Verres needle. Though greater than the rate of 1–1·3% reported for the insertion of temporary catheters in peritoneal dialysis patients (Leehey *et al.* 1982) it is in keeping with the more representative rate of 10% of bowel perforation that can occur at second-look laparoscopy in ovarian cancer patients (Berek *et al.* 1981). Temporary catheter placement, though safe, is neither straightforward nor reliable.

It is not possible from our data to assess which of the two approaches for peritoneal access is better as they were used in dissimilar patient groups and for different reasons. Nevertheless this paper illustrates that in ovarian cancer patients there are problems with achieving reliable repeated access to the peritoneal cavity using either permanent or temporary peritoneal catheters, although nearly all of the complications observed in the temporary catheter group were associated with the use of the Venflon intravenous cannula which is too short and sharp. Unless these problems can be overcome the potential advantages of intraperitoneal therapy and monitoring will not be realized.

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Division of uterine adhesions (Asherman's syndrome) with the Nd-YAG laser

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Summary. Two women with Asherman's syndrome after postpartum curettage are presented. The diagnosis was confirmed by hysteroscopy. The adhesions were vaporized under hysteroscopic control, using a Nd-YAG laser (neodymium-yttrium-aluminium-garnet laser). The method was precise, casued minimal thermal injury and resulted in immediate return of regular menstrual cycles. The use of the Nd-YAG laser for Asherman's syndrome warrants further study.

Asherman's syndrome (amenorrhoea traumatica), first described by Asherman (1948), is a condition in which intrauterine adhesions develop leading to partial or complete obliteration of the uterine cavity and or cervical canal. The condition may occur after uterine curettage, subsequent to delivery or abortion, the main aetiological factors being trauma and infection. The diagnosis of the condition is suggested by the history, development of amenorrhoea and confirmed by hysterosalpingography, hysteroscopy, or both. A variety of methods have been used to divide the uterine adhesions including: blind, sharp curettage (Asherman 1948; Klein & Garcia 1973), hysteroscopic directed division with diathermy or scissors (Lancet & Mass 1981), or hysteroscopic directed curettage (Sanfilippo *et al.* 1982). In some series this has been followed by placement of an intrauterine device and cyclical hormones (Sanfilippo *et al.* 1982), or the use of a paediatric Foley catheter to distend the cavity with or without hormone therapy (Klein & Garcia 1973).

We report the successful treatment of two patients with Asherman's syndrome, who had complete amenorrhoea secondary to postpartum curettage.

Patients and methods

The first patient was a 28-year-old woman who had an abortion induced with extra-amniotic prostaglandin because of a fetal neural tube defect. Two weeks after the abortion she had a curettage because of continuous vaginal bleeding. For the subsequent year she had complete amenorrhoea. All hormonal investigations, including follicle-stimulating hormone, luteinizing hormone, oestradiol, testosterone and prolactin, were normal. Despite treatment with clomiphene and ethinyloestradiol there was no return of menstruation. Hysterosalpingography showed no filling of the uterine cavity. Hysteroscopy demonstrated intrauterine adhesions and almost complete obliteration of the uterine cavity and partial obliteration of the cervical canal.

The second patient was a 33-year-old woman who had several postpartum curettages performed in Venezuela because of postpartum bleeding. Following this she had complete amenorrhoea. Investigation 6 months later in the UK by hysterosalpingography showed no uterine cavity, and hysteroscopy confirmed the presence of intrauterine adhesions. Follicle-stimulating hormone, luteinizing hormone, pro-

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lactin, oestradiol and testosterone were all within normal limits.

Instruments used

Laser vaporization. The uterine and cervical adhesions were vaporized using a laser beam generated by a neodymium-yttrium-aluminium-garnet laser (Nd-YAG) which has a wavelength in the infrared spectrum and hence uses a He Ne (helium neon) tracking low-power laser to aim the beam. The Pilkington Fibrelase 100 system used for this study generated 50 to 100 W with a light pulse range of 0 to 9·9 s. The laser light was transmitted from the laser port to the patient through a two-core fibre-optic cable, the outer core was paired back to the length of the hysteroscope and the inner core removed from the distal 10 mm of cable. This inner core was threaded through the hysteroscope and used to place the laser beam against the adhesions.

Hysteroscope. A Storz modified hysteroscope, constant flushing adaptation of a standard paediatric nephroscope, was used with a fluid medium (Dextran 70) to distend the uterine cavity. The constant flushing and suction was necessary to maintain a clear view during laser vaporization and the modified hysteroscope was fitted with an operating channel down which the fibre-optic cable was passed.

The procedure. The patient was prepared as for standard operative hysteroscopy. The hysteroscope was advanced under direct vision and the laser optical fibre applied to each adhesion which was then vaporized. The hysteroscope was then advanced and the procedure repeated until the cervical canal and uterine cavity were completely open and both tubal ostia could be seen. Due to the properties of the laser light, bleeding was minimal and the little capillary oozing was easily controlled by the irrigating fluid.

In our first patient, a power level of 40 W was used, the duration of each pulse was 2 s to a pulse total of 8 (i.e. 16 s). The total energy delivered was 423 J. This was sufficient to vaporize all cervical and uterine adhesions to open up the whole of the uterine cavity. There was no bleeding and 100 ml of irrigating fluid were used. A Lippes loop size C was inserted at the completion of the procedure as the patient wished to use this for contraception. This has been retained beyond the first 6-week follow-up appointment.

In our second patient the power level was 35–40 W, each pulse was of 2 s duration with a pulse total of five. The total energy delivered was 267 J. This was sufficient to vaporize all cervical and uterine adhesions. There was no bleeding and 100 ml of irrigating fluid were used. A Lippes loop size C was not inserted as a suspected partial perforation of the uterus occurred on passing a uterine sound after laser vaporization and before insertion of the Lippes loop.

Follow-up

Within 1 month there was prompt return of menstruation in both women. They now have regular cycles with normal flow every 28 to 30 days up until the time of reporting (at 8 months follow-up).

Discussion

Asherman's syndrome is rare and the clinical picture and degree of adhesion formation are variable, ranging from a few intracervical adhesions to complete obliteration of the uterine cavity. In a review of the literature, Klein & Garcia (1973) indicated the difficulty in assessing the efficacy of treatments described in 19 papers due to the variable degree of adhesion formation. Bergman (1961) suggested that the frequency of adhesions may be as high as 20% in women who have an early postpartum curettage, while Dnowski & Greenblatt (1969) found the frequency of adhesions to be 1·5% in all patients having a hysterosalpingogram (HSG). This frequency rose to 39% when patients were selected for HSG on the basis of history and examination.

Early work relied on the history and X-ray hysterography (Dnowski & Greenblatt 1969), uterine sounding to detect adhesions (Behrman & Kistner 1968), hormone withdrawal tests (Behrman & Kistner 1968), or a diagnostic dilatation and curettage (Klein & Garcia 1973). More recently hysteroscopy, either alone (Sanfilippo *et al.* 1982), or in conjunction with hysterography (Lancet & Mass 1981), has been used to confirm the diagnosis.

The history usually is of secondary amenorrhoea, infertility and possibly cyclical pain, or menstrual irregularities. These symptoms are often preceded by postpartum or postabortal curettage or multiple curettages. In addition to trauma as an aetiological factor there is often evidence of infection, an infected abortion or retained products (Klein & Garcia 1973).

The methods used to divide these adhesions have been varied and often combine more than one method. Initially blind, sharp curettage and uterine sounding was used (Asherman 1948; Ismajoich *et al.* 1985), hysterotomy and sharp dissection of the adhesions (Asherman 1957), sharp curettage with or without hysteroscopy (Sanfilippo *et al.* 1982), hysteroscopically directed division of adhesions with either diathermy or with flexible scissors (Lancet & Mass 1981), and now, with our study, the Nd-YAG laser. The YAG laser has obvious advantages. It is relatively easy to use, precise in the amount of tissue (adhesions) destroyed, involves minimal thermal damage and therefore is less likely to cause postoperative recurrence of adhesions. It causes little intra-operative bleeding. In order to obtain a clear view a fluid distension medium is needed, such as Dextran 70, rather than carbon dioxide gas. In addition a constant flushing hysteroscope, such as the model we have developed with Storz, allows adequate immediate removal of carbon particles left after laser vaporization and maintains the clear view. The use of the Nd-YAG laser allows a flexible fibre-optic bundle to be used to place the laser beam accurately on the adhesion to be vaporized. When coupled with the manipulating arm on the hysteroscope, the tip of the fibre-optic cable can be made to reach all aspects of the uterine cavity.

Postoperative cavity distension to allow endometrial healing has utilized either an intra-uterine device (Klein & Garcia 1973; Lancet & Mass 1981; Sanfilippo *et al.* 1982), or a paediatric Foley catheter (Klein & Garcia 1973). These have been left in place for a few days to 4 weeks. In some series this treatment is supplemented by the addition of cyclical hormone therapy for a few months (Klein & Garcia 1973; Lancet & Mass 1981; Sanfilippo *et al.* 1982). However, similar results have been observed without hormone therapy (Ismajoich 1985).

The lack of tissue damage with the Nd-YAG laser, easy division of adhesions and the prompt return of regular menstrual cycles in our patients warrants further study. However, the advantages of this method of treatment for Asherman's syndrome with precise destruction of adhesions under hysteroscopic control and little thermal damage to surrounding tissues do allow an easy and specific surgical treatment for this condition. It may also obviate the need for postoperative adjunctive therapy.

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The place of laparoscopy in women with ascites

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Summary. Laparoscopy was performed in 70 women with ascites of unknown origin, and in 56 a visual diagnosis, aided by biopsy, was made. There was carcinoma in 32, tuberculosis in 20 and cirrhosis of the liver in four. No abnormality was seen in 14.

Ascites is encountered frequently in gynaecological practice although most patients are referred to the gynaecologist by physicians or gastroenterologists. Particularly where diagnostic ultrasound is unavailable, laparoscopy offers a valuable and relatively simple aid to diagnosis.

Patients and methods

Between January 1975 and July 1987, 70 women aged between 18 and 70 years, with ascites of unknown origin, were subjected to diagnostic laparoscopy at the King Edward Memorial Hospital and Sir Hurkisondas Hospital, Bombay. Of these, 60 were already in-patients, and 54 had been referred by physicians and gastroenterologists. The major presenting complaints, detailed in Table 1, were generally non-specific.

Pre-operatively each patient was fully investigated by blood and urine examinations, chest radiography, ECG, liver and renal function tests and barium studies. Fitness for general anaesthesia was assessed by an anaesthetist. Four to 12 h before laparoscopy, the abdomen was tapped and 1000–2500 ml of ascitic fluid removed.

Anaesthesia

General anaesthesia was given to 50 women; the remaining 20 were considered to be at 'mild to moderate risk' because of cardiopulmonary impairment and a smaller instrument or needlescope was then used with local anaesthesia.

Laparoscopy

All laparoscopies were performed by the author, 12 jointly with the gastroenterologists. The usual technique was employed with some modifications. An exaggerated head up and head down position was used to give a better view of the upper abdomen and pelvis; where additional tapping of ascitic fluid was needed during laparoscopy, a Verres needle was introduced into the pouch of Douglas through the vagina

Biopsies were taken from 54 women, and ascitic fluid was collected for biochemistry, cytology, culture and guinea-pig inoculation.

The incision was closed in two layers to minimize postoperative seepage of ascitic fluid.

Investigation with the 2·2-mm needlescope in 20 women took from 7 to 10 min longer than with the larger laparoscope but the findings were positive in 17 women, 10 had malignancies, four had tuberculosis and three had cirrhosis of the liver.

Results

It was not possible to see the whole abdomen in 64 of the 70 women because residual fluid obscured the view, but a positive diagnosis was possible in 56. In 14 no abnormality was found.

The detailed findings related to presenting features and final diagnosis are presented in Table 1.

Malignancy

In 32 women there was a strong suspicion of malignancy and in two other women ovarian malignancy was thought to be possible. Biopsies were not taken from these two women because the ovarian capsules were intact, but subsequent examination after hysterectomy revealed that one had a malignant granulosa cell tumour and the other had a fibroma of the ovary; retrospec-

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Table 1. Details of patients with ascites

	Diagnosis			
	Malignancy (n=32)*	Tuberculosis (n=20)	Cirrhosis (n=4)	No cause found (n=14)
Age (years)				
<30	2	7	1	4
31–50	19	10	3	9
51–60	8	1	0	1
61–70	3	2	0	0
Presenting symptoms				
Abdominal enlargement	32	20	4	14
Abdominal discomfort/pain	26	8	2	4
Loss of weight	10	13	4	3
General weakness	24	12	3	7

*Includes two patients with Meig's syndrome, one due to granulosa cell tumour and the other due to fibroma of the ovary.

tively both were categorized as Meig's syndrome. In two women the histological diagnosis was tuberculosis.

Tuberculosis

Twenty women had a diagnosis of tuberculosis this was suspected at laparoscopy in 18, but in the other two malignancy was suspected at first. The appearance varied from widespread miliary spread, a few tubercles with areas of caseation, calcification, to large matted lesions and widespread adhesions. Of the 20 women with tuberculosis, the disease affected pelvic structures in 16, of whom 12 also showed extensive abdominal involvement. In all 20 women the diagnosis was confirmed by histology, but of 16 cultures for acid-fast bacilli only eight were positive, and all 12 guinea-pig inoculations were negative.

Discussion

Although laparoscopy has been little used in Europe and North America in the management of ascites of unknown origin, it has been used extensively in India, but more by general surgeons than by gynaecologists.

Of 2500 peritoneoscopies reported by Udwadia (1986), the indication in 507 was ascites. As in the present study, the main causes were malignancy (215), tuberculosis (178) and cirrhosis of the liver (61). He also found that demonstration and culture of acid fast bacilli was rare, making histological diagnosis essential.

Ascites was once thought to be a relative contraindication to laparoscopy but experience has proved otherwise (Borten 1986). Bowel injury, particularly, must be guarded against. Not only does the bowel float on top of the ascitic fluid (Udwadia 1986), but there is a high risk of intraperitoneal adhesions to the anterior abdominal wall, particularly if the ascites is due to tuberculosis. In fact, tuberculous peritonitis has been considered an absolute contraindication to laparoscopy (Phillips 1977; Holt 1984). Bowel injury did not occur in the present study and only once in the 2500 peritoneoscopies reported by Udwadia (1986).

Laparoscopy and biopsy offer a quick and accurate diagnosis in patients with unexplained ascites, and is particularly useful in countries where tuberculosis is a common cause and where sophisticated non-invasive diagnostic techniques are not available. It will also allow many laparotomies to be avoided.

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Clinical characteristics of subfertile men with antisperm antibodies

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Summary. This study investigated the clinical features which could serve as markers to identify subfertile men with antisperm antibodies including age, duration of infertility, history of abdominal or perineal surgery and previous genital trauma. Of the 162 men studied, 43 had a positive test for antisperm antibodies. A significantly greater number of these patients had a history of genital trauma and appendicectomy. Whereas the aetiological role of genital trauma in spermatozoal autoimmunity is readily explicable, that of appendicectomy is not. It can only be postulated that inflammation of the appendix may sometimes affect the vas deferens or that there is some inadvertent injury to the vas deferens during appendicectomy.

It is now generally accepted that antisperm antibodies can be a cause of male infertility (Rumke *et al.* 1974; Hendry *et al.* 1977; WHO 1984; Bronson *et al.* 1984).

Research over the last three decades has unravelled some of the mechanisms of sperm antibody-mediated infertility, which include: impaired sperm penetration through cervical mucus (Kremer & Jager 1976, 1981), increased sperm attrition in the female genital tract and exclusion of viable sperm from the site of fertilization (Adeghe 1987*a*), and inhibition of sperm penetration into human ova (Bronson *et al.* 1982). Clinical management of this subgroup of infertile men still remains unsatisfactory.

One fundamental problem in many infertility clinics is the lack of pragmatic methods for identifying men with immune-based infertility. There is often reluctance to test routinely for antisperm antibodies because of the argument that the prevalence of antisperm antibodies is low, and that testing everyone is not cost-effective. Many clinicians selectively test men who show signs, symptoms and history suggestive of spermatozoal autoimmunity. In an earlier study, we found no characteristic of seminal fluid analysis that could effectively identify those men with antisperm antibodies, but we did not examine other clinical features which could serve as markers to identify subfertile men with antisperm antibodies.

Hendry *et al.* (1977) described the couple with immunological infertility as typically having a long history of infertility and with predisposing factors such as vasectomy, vasectomy reversal, inguino-perineal trauma or surgery, mumps orchitis or genital infection.

The role of vasectomy in the causation of antisperm antibodies is well established in man (Ansbacher 1973; Linnet *et al.* 1981; Royle *et al.* 1981) and other animals (Alexander *et al.* 1974; Alexander 1977; Lucas & Rose 1978; Samuel & Rose 1980), as is that of genitourinary tract

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infection (Fjallbrant & Nilsson 1977; Witkin & Toth 1983; Shamanesh *et al.* 1986). As far as we know, no definite study has attempted to ascertain whether the presumed relation between genital trauma or previous abdominal/inguinal surgery and antisperm antibodies is real or spurious.

The present report compares the age, duration of infertility, history of genital trauma and abdominal/inguinal surgery in subfertile men with or without antisperm antibodies.

Patients and methods

Data from 167 men investigated for infertility were studied retrospectively. All the men were tested for the presence of sperm surface antibodies as part of routine semen analysis. On their first visit to the laboratory, each man was questioned systematically, and the following details were recorded: age, duration of infertility, any history of abdominal or perineal surgery and any previous significant trauma which caused painful local swelling in the genital area and/or required medical attention.

Each man produced a sample of semen for testing after 3 days of sexual abstinence. Ejaculates were produced in a room close to the laboratory and allowed to liquefy for 1 h at 37°C. The semen sample was washed twice in 1% human serum albumin (HSA) in phosphate-buffered saline (PBS) by centrifugation at 600 *g* for 5 min and finally resuspended to give a concentration of about 10^6/ml. Washed spermatozoa were tested for presence of surface IgG and IgA antibodies using the immunobead test as described previously (Adeghe 1987*b*). Briefly, lyophilized IgG and IgA-immunobeads (Bio-rad Labs, Watford, UK) were each dissolved in PBS (pH 7·3) to a concentration of 2 mg/μl. The test was performed by mixing 5 μl of sperm with 25 μl of isotype-specific immunobead suspension on each of two glass slides and covering with a 22 mm×22 mm coverslip. These were incubated at room temperature for 5–10 min and examined at ×400 magnification under phase-contrast. A total of 400 motile spermatozoa (200 on each slide) was scored and the result expressed as the proportion (percentage to the nearest 5%) binding to one or more immunobeads. A positive result was regarded as 10% or more of sperm binding to immunobeads (IgG and/or IgA).

The cut-off point of 10% between a positive and a negative immunobead test was chosen because larger studies in our laboratory (Adeghe *et al.* 1986) and in the USA (Bronson *et al.* 1981) have shown that non-specific sperm binding of <10% can be obtained in normal men of proven fertility.

Statistical analysis

Mean age and duration of infertility in the two groups were compared using probability related to standard error. All other comparisons between the groups used the χ^2-test with Yates' correction.

Results

At the time of analysis of the data 167 patients had been tested for antisperm antibodies. Five of these patients had previous vasectomy reversals and were therefore excluded from further analysis.

Of the remaining 162 patients, 43 had sperm surface antibodies (IgG and/or IgA) (ASA+ve) while the remaining 119 had a negative antisperm antibody test (ASA−ve). Table 1 compares the prevalence of genital trauma, appendicectomy, orchidopexy (for undescended testis), inguino-perineal operations (e.g. inguinal hernia repair) between the antibody-positive and antibody-negative groups and also the mean age and duration of infertility.

The proportion of men in the antibody-positive group with the history of significant trauma and appendicectomy was significantly greater than that in the antibody-negative group. There was no significant difference in the mean age, duration of infertility and proportion with previous orchidopexy between the two groups.

Discussion

The direct immunobead test is of utmost clinical relevance since it tests for antibodies on 'the target organ' (the sperm surface membrane). It is now generally accepted that antibodies present locally in semen (especially on the sperm surface) are more relevant to fertility impairment than those present systemically in blood serum. The immunobead test is one of the most sensitive and specific tests for sperm surface antibodies (Clarke *et al.* 1985) and is highly recommended for clinics setting up tests for antisperm antibodies.

Spermatozoa develop after 'self'-recognition

Table 1. Clinical characteristics of subfertile men with or without antisperm antibodies

Factor	Antibody-positive (n=43)	Antibody-negative (n=119)	Significance	
			χ^2	P
Genital trauma	11	2	21·35	<0·001
Previous appendicectomy	7	4	6·412	<0·02
Orchidopexy	0	4	0·153	>0·50
Inguino/perineal operations	3	2	1·456	>0·10
Age (years) mean (SD)	35·1 (5·89)	34·2 (4·84)	—	≃0·317*
Duration of infertility (years) mean (SD)	4·7 (3·16)	5·5 (3·10)	—	>0·10*

*Probability related to multiples of standard errors.

in the immune system has occurred, therefore the immune system in each individual would regard sperm as immunologically foreign. It is generally accepted that spermatozoa are sequestrated from the individual's own immune system by tight junctions (blood–testis barrier) between the serotoli cells in the testis (Setchell 1967; Waites & Setchell 1969). Disruption of this barrier in the male reproductive tract therefore is likely to risk exposure of the sperm to the immune system and lead to antisperm antibody formation. Against this background, it is not surprising that genital trauma may lead to antisperm antibody formation. In fact this relation is so predictable that many authors have accepted it without supporting evidence. We recognize that there are varying degrees of trauma, and our study provides the first evidence that significant trauma (defined as that which is serious enough to cause local swelling and/or required medical attention) is indeed important in the causation of spermatozoal autoimmunity. In our study genital trauma was generally sustained from kicks (during fights or ball games), falls from bicycles and motor car accidents occurring after puberty.

Perhaps more interesting is the relation between previous appendicectomy and the formation of antisperm antibodies. This is not easily explicable, but one hypothesis is that the vas deferens has a close anatomical relation to the site of operation and therefore may suffer unrecognized damage which leads to escape of sperm cells.

Another possibility is that the inflammation of the appendix may extend locally and involve the spermatic cord leading to increased permeability of the wall of the vas deferens. Larger studies will be needed to discover the true prevalence and the exact mechanism for eliciting formation of antisperm antibodies in patients who have had an appendicectomy.

We did not find any difference in the mean duration of infertility between the antibody-positive and antibody-negative groups, in contrast to Hendry *et al.* (1977) who reported that patients with immune-based infertility presented with a longer history of infertility than those with other causes.

The usual clinical findings which increase the suspicion of the presence of antisperm antibodies are a poor postcoital test (Bronson *et al.* 1984), poor penetration of cervical mucus (Morgan *et al.* 1977) and agglutination of spermatozoa.

In addition to these factors our study clearly shows that subfertile men with a history of genital trauma and appendicectomy are at a significantly greater risk of developing antisperm antibodies. We therefore recommend that subfertile men with a history of vasectomy reversal, genital trauma and appendicectomy should be tested for antisperm antibodies, using the immunobead method, to exclude these as a cause of subfertility.

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Primary malignant Schwannoma of the uterine cervix. Case report

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Case report

A 45-year-old woman with two deliveries 20 and 17 years previously was referred to a gynaecologist after 2 weeks of vaginal bleeding. Under examination a polypoid red tumour measuring 1 cm was seen on the posterior lip of the cervix uteri. A biopsy was taken and histological investigation revealed a malignant tumour of uncertain origin for which a hysterectomy with pelvic lymph node biopsies was performed.

At operation no tumours were observed in the abdominal or pelvic cavity. The tubes and ovaries appeared normal. The postoperative course was uneventful.

Methods

The cervix uteri including the tumour was cut in sagittal sections and was completely embedded These specimens and several sections from the remaining uterus and the parametria were investigated.

For light microscopy the sections were stained with haematoxylin and eosin, van Gieson, chromotrophic Aniline blue, Bodian, Gordon and Sweets reticulin and Lillie's ferrous ion uptake for melanin.

For immunohistochemical investigation additional sections cut from the paraffin blocks were incubated with antibodies against Vimentin, S-100 protein, Desmin (all from Dacopatts, DK), and cytokeratin (Becton-Dickinson). The conventional immunoperoxidase technique and the Avidin-biotin-peroxidase complex method were used including positive and negative control reactions for each antibody.

For electron microscopic examination fresh tumour tissue cut into 1 mm^3 cubes was fixed in Karnovsky's fixative (Karnovsky 1965) and embedded in Epon. Survey sections, 1 μm thick, were stained with toluidine blue, and ultrathin sections were stained with uranyl acetate and lead citrate and examined in a JEOL 100 electron microscope.

Pathology

The surgical specimen was a 8·5 × 6 × 5 cm large uterus without any adnexa. In the posterior lip of the cervix a large (12 × 10 × 10 mm), non-encapsulated, rounded tumour with a greyish-red cut surface with haemorrhage and necrosis was seen (Fig. 1). The endometrium and the myometrium were macroscopically normal.

Light microscopy

The tumour was composed of solidly arranged spindle cells occasionally occurring in fascicles and wavy bundles and partly in a storiform-like pattern (Fig. 2). In some areas the tumour was less cellular with a microcystic pattern (Fig. 3) The nuclei were plump, ovoid with variation in chromatin density and were surrounded by faintly stained eosinophilic cytoplasm with indistinct cell borders Scattered mitoses were seen Small foci of necrosis and haemorrhage were noted throughout the tumour which was ulcerated along the portio surface and exhibited an infiltrative growth pattern in the deeper portions of the cervix (Fig. 4) Small bundles of collagen were present in the tumour, and the single tumour cells were surrounded by delicate fibrils

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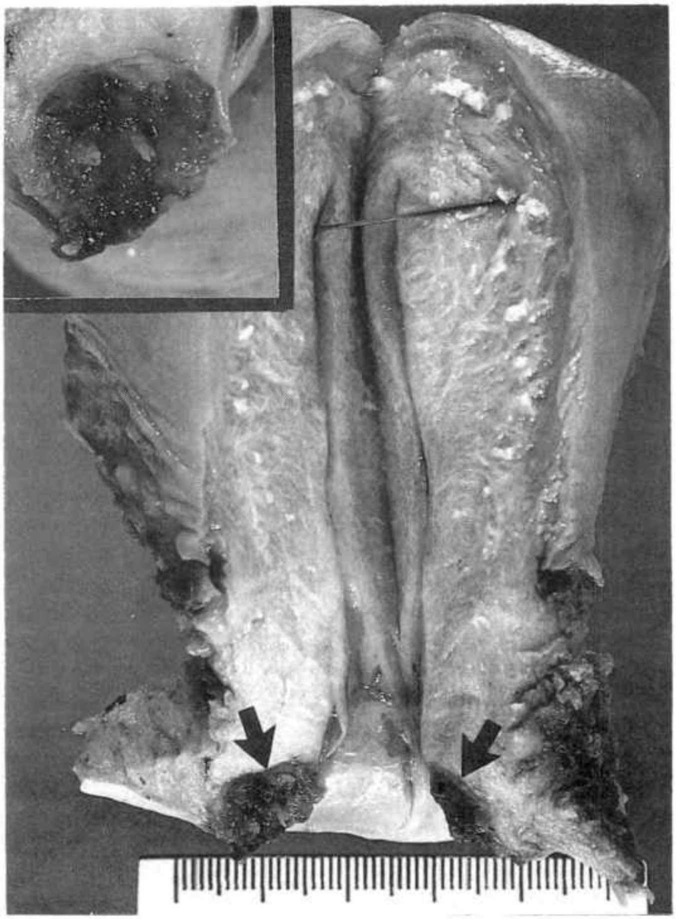

Fig. 1. The surgical specimen opened from behind. The tumour (arrows) is seen in the posterior wall of the cervix. Insert: closer view of the tumour cut surface with haemorrhage. Note the irregular demarcation.

positive in the reticulin-stained sections. The Bodian staining and the reaction for melanin pigment were negative.

The pelvic lymph nodes showed no metastases.

Immunohistochemistry

Only scattered tumour cells expressed positivity for S-100 protein. Numerous tumour cells were positive for Vimentin, while both Desmin and cytokeratin failed to stain at all.

Ultrastructure

Tumour cells were closely packed with only little collagen between cells. The cytoplasm showed intertwining processes and infoldings joined by intercellular junctions (Fig. 5). The cell surfaces were covered by a more or less continuous basal lamina (Fig. 6). In the cytoplasm an inconspicuous organel apparatus with scattered lysosomes and myelin figures was seen. No secretory granules or melanosomes were encountered. No Luze-bodies were identified in the stroma.

Discussion

Malignant Schwannomas are derived from peripheral nerve sheaths (Ducatman *et al.* 1986; Enzinger & Weiss 1983). They are rare neoplasms which may be associated with von Recklinghausen's neurofibromatosis (Guccion & Enzinger 1979) or may arise as solitary independent malignant Schwannomas (Enzinger & Weiss 1983; Das Gupta & Brasfield 1970).

Malignant Schwannomas are often located on

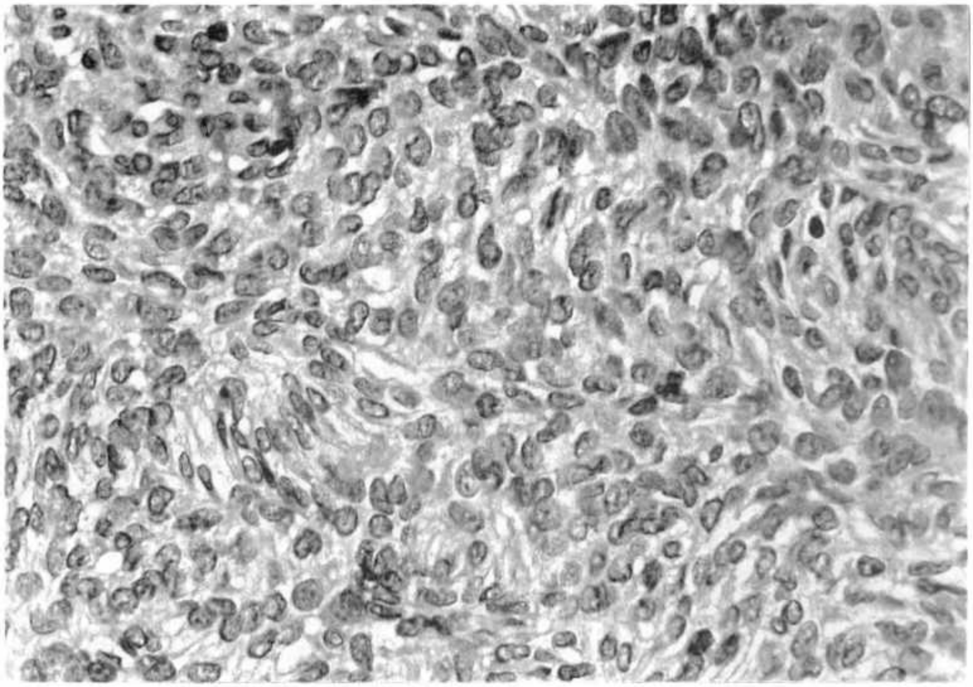

Fig. 2. Light microscopic specimen showing solidly arranged, plump spindle cells with Antoni A-like pattern. Haematoxylin and eosin. × 400.

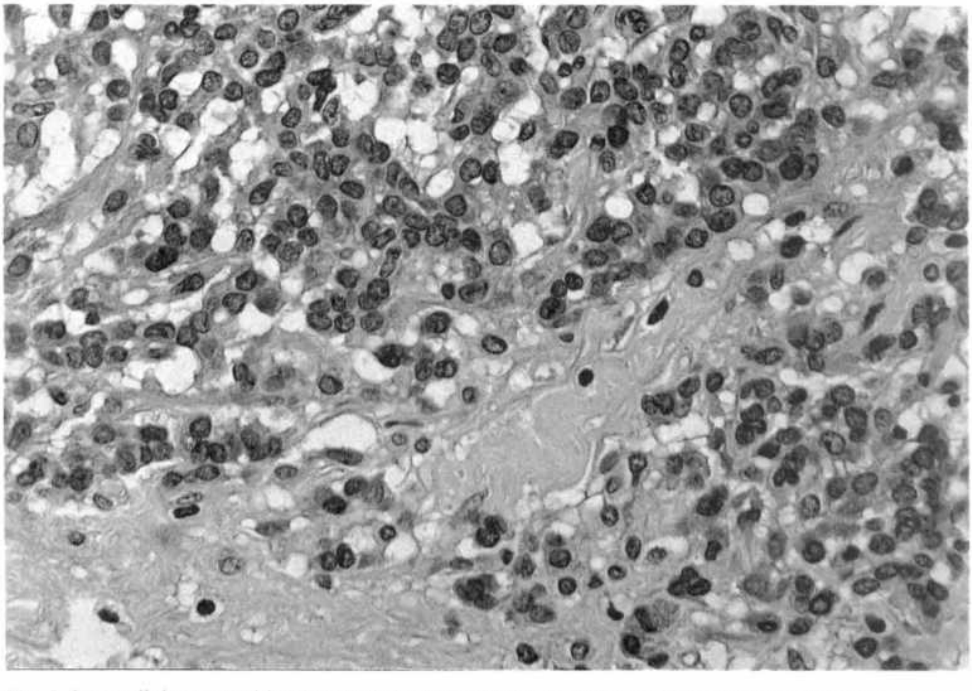

Fig. 3. Less cellular area with microcystic background (Antoni B-like pattern). Haematoxylin and eosin. × 400.

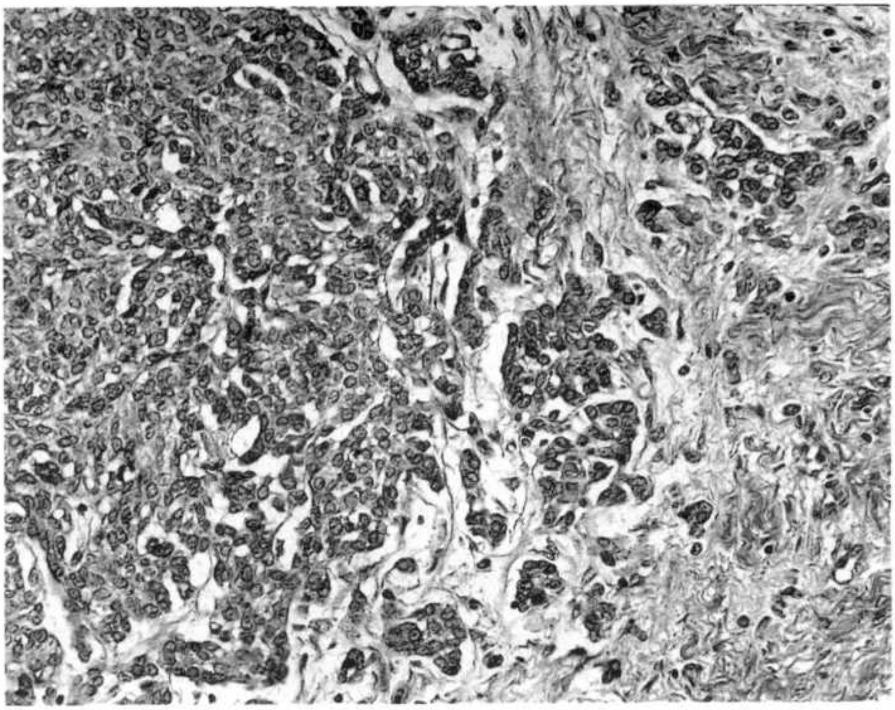

Fig. 4. Cellular area of the tumour with infiltrative growth along the periphery. Haematoxylin and eosin. × 250.

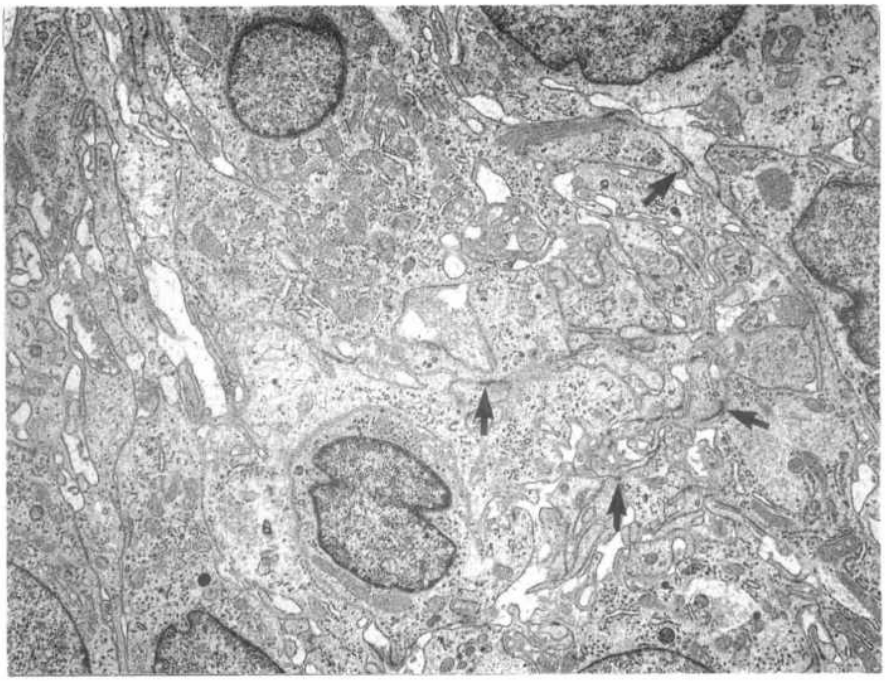

Fig. 5. Electron micrograph showing tumour cells with cytoplasmic extensions and infoldings. Several intercellular junctions are seen (arrows). × 2000.

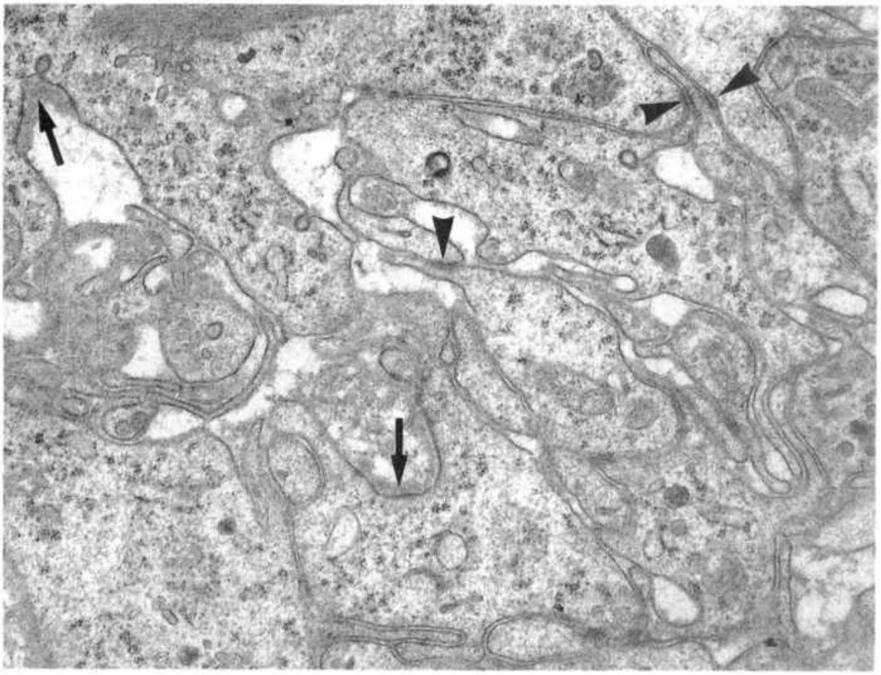

Fig. 6. Electron micrograph revealing cellular processes covered with abundant basal lamina material (arrows). Intercellular junctions: arrow heads. × 10 000.

the extremities, in the head and neck region, in the trunk and in the paravertebral regions (Ducatman *et al.* 1986; Guccion & Enzinger 1979). Other rarer sites of origin have been reported (Das Gupta & Brasfield 1970; Lederman *et al.* 1987).

In this article we present an unusual case of primary malignant Schwannoma in the uterine cervix in a 45-year-old woman without von Recklinghausen's disease. To our knowledge a malignant Schwannoma has not previously been reported in this location.

Primary sarcomas of the uterine cervix are rare and these neoplasms are most often registered as leiomyosarcomas, embryonal rhabdomyosarcoma and fibrosarcoma (Poulsen *et al.* 1975).

We report here the first case of a primary malignant Schwannoma in the uterine cervix. Examination by light microscopy alone was inconclusive although areas exhibiting both Antoni A and Antoni B-like patterns (Enzinger & Weiss 1983) could be recognized in the hysterectomy specimen (Figs 2 & 3).

From investigations with the light microscope alone, a fibrosarcoma, a leiomyosarcoma, a malignant fibrous histiocytoma, a monophasic synovial sarcoma, a rhabdomyosarcoma (Enzinger & Weiss 1983; Das Gupta & Brasfield 1970; Ducatman *et al.* 1986) and even a spindle squamous cell carcinoma and a malignant melanoma were initially considered as possible differential diagnoses to a malignant Schwannoma.

Immunohistochemical analysis showed the mesenchymal origin of the tumour (Vimentin positive and cytokeratin negative (Wick *et al.* 1987)) and the presence of scattered S-100 positive cells was strongly in favour of a Schwann cell tumour (Weiss *et al.* 1983; Wick *et al.* 1987).

The ultrastructural findings, i.e. the presence of extensive intertwining cell processes, scattered intercellular junctions and a prominent basal lamina, are highly characteristic and diagnostic for a Schwann cell tumour.

The malignant nature of the present tumour was judged from the infiltrative growth pattern and from areas with necrosis and haemorrhage (Woodruff *et al.* 1981; Enzinger & Weiss 1983). In these respects the tumour differs from the 'cellular Schwannoma', which is a benign entity showing both mitotic activity and cellular pleomorphism (Woodruff *et al.* 1981; Fletcher *et al.* 1987). Benign Schwannomas including cellular Schwannomas are characteristically strongly S-100 positive whereas malignant varieties may be negative or only weakly positive (Weiss *et al.* 1983). The finding of only scattered S-100 positive cells thus supports the malignant nature of the present case.

Peripheral nerve trunks are present in the uterine cervix and it is therefore not surprising that malignant Schwannoma may develop in this location. A benign Schwannoma has previously been reported in the cervix uteri (Gwavava & Traub 1980), and blue naevi supposedly also deriving from Schwann cells (Kudo *et al.* 1983) have been described.

Whether the few cases of malignant Schwannoma reported in the literature reflect the true incidence of this tumour entity is questionable. The increasing use of electron microscopy and immunohistochemistry in the diagnostic work-up of benign and malignant neoplasms may show these tumours to be more common than hitherto assumed. The present case thus emphasizes the importance of electron microscopy and immunohistochemistry in the interpretation of tumours of uncertain origin.

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Vaginal ultrasound for ruling out placenta praevia. Case report

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Case report

The 33-year-old patient was in her fifth pregnancy, her obstetric history included a miscarriage, two normal pregnancies and deliveries, and an uncomplicated abortion. She had a transabdominal sonograph (TAS) with a 3·5 MHz linear probe at 27 weeks and confirmed her dates. The placenta was posterior, and a grade II placenta praevia was suspected. The fetal position was oblique and the fetal head was out of the pelvis. The patient was unable to maintain a full bladder for the TAS. The possibility of placenta praevia was discussed with the patient, and she was discharged home according to our routine which is similar to the one described by Silver *et al.* (1984). Six weeks later, at 34 weeks, the patient had some spotting and 2 days later one episode of brisk vaginal bleeding. She was admitted for observation. There was no subsequent bleeding. The non-stress tests were reactive. Her haemoglobin was 10·7 g/dl. The haematocrit was 31·1% and other laboratory investigations were normal.

A second TAS on admission (Fig. 1) revealed adequate fetal growth and a grade III placenta praevia with a retroplacental clot close to the internal os. The fetal head was engaged in the pelvis. Transvaginal sonography was performed the next day (Fig. 2). The internal os could be seen and was not covered by the placenta, which was found to be posterior and 2–4 cm from the internal os. Following this diagnosis the patient was discharged home to be followed in the clinic. She had an uneventful vaginal delivery at 38 weeks.

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Discussion

Transabdominal sonography (TAS) is currently the only commonly used method for diagnosing placenta praevia (Gottesfeld *et al.* 1966). TAS diagnosis of placenta praevia has several inherent problems. A full bladder, needed for good identification of the low-lying placenta, may compress the placenta and result in a false diagnosis of placenta praevia (Williamson *et al.* 1978). A posterior placenta, as in the present case, or even a lateral placenta is less well displayed by the abdominal route than an anteriorly located placenta (Edlestone 1977). The fetal head in vertex presentation may prevent appropriate imaging of placenta praevia (King 1973). The later in gestation the scanning is done the greater is the acoustic shadowing of the head, due to the progressive thickening of the fetal skull. Because of the small size of the uterus and its lower segment in mid-pregnancy, 90% of patients diagnosed to have placenta praevia in mid-pregnancy will not have the same diagnosis at term (Wexler & Gottesfeld 1973).

For the reasons mentioned above, TAS may result in a false-positive diagnosis of placenta praevia. Women who were diagnosed to have placenta praevia, but in fact did not, may undergo several unnecessary sonographic examinations, may have unnecessary hospitalization, and may be delivered by an unnecessary caesarean section Being aware of a possible false-positive diagnosis, women with suspected placenta praevia are often exposed to a vaginal

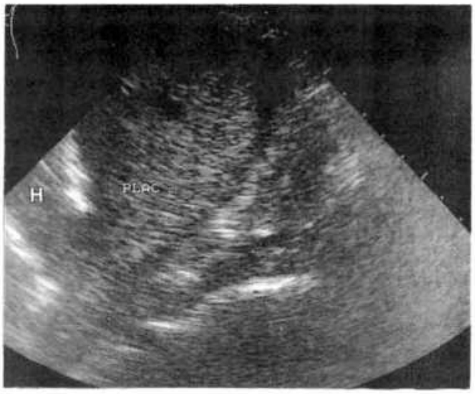

Fig. 1. Transabdominal sonography of a patient suspected of a placenta praevia. The cervix is on the right side of the picture. The exact location of the cervical canal and the internal os can not be outlined in this picture. The placenta and the fetal head (H) are well imaged. Diagnosis of placenta praevia was made by this route.

examination under anaesthesia to rule out the presence of placenta praevia. This examination exposes the patient to the risk of a major haemorrhage and to the unnecessary risks of general anaesthesia if an emergency caesarean delivery is indicated.

Until recently there was no other method (besides vaginal examination) to which abdominal ultrasound could be compared. A recent paper showed that magnetic resonance imaging (MRI) is superior to abdominal ultrasound in diagnosing placenta praevia and its extent (Powell *et al.* 1986). Even if MRI is found to diagnose placenta praevia accurately, its use could be limited by its high cost and availability only to major centres.

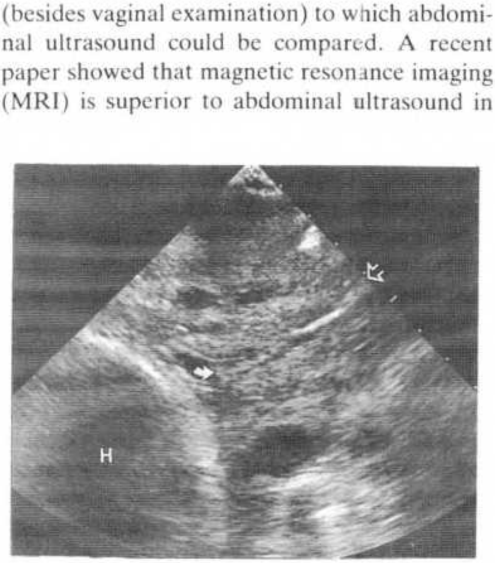

Fig. 2. Transvaginal sonography of the same patient on the same date. The cervical canal is clearly seen. The external os is marked by the open arrow. The internal os is marked by the solid arrow. The head (H) was well applied to the internal os. The diagnosis of placenta praevia was ruled out.

In recent years transvaginal sonography (TVS) has been developed to produce a high resolution picture of the pelvic organs (Timor-Tritsch & Rottem 1987). The sound travels a shorter distance from the tip of the vaginal probe to the pelvic organs than from the tip of the abdominal probe. This enables the use of a higher frequency ultrasound wave generator of 5·0–7·0 MHz, which in turn increases the resolution of the picture (Thaler *et al.* 1987; Timor-Tritsch *et al.* 1988). The role of the vaginal probe is well established in diagnosing early pregnancy, ectopic pregnancy, pelvic masses and other pelvic pathologies (Timor-Tritsch *et al.* 1987).

According to classical obstetric teaching, there is an apparent risk of bleeding following vaginal manipulation of a bleeding pregnant patient in the second or third trimester (Pritchard *et al.* 1985). However, the vaginal probe is introduced slowly into the vagina under direct sonographic demonstration of the cervix. The tip of the probe stops short of the cervix because a clear picture is produced when the distance between the probe and the cervix is about 3 cm. One should remember that the effective 'focal zone' of a 5 or 6·5 MHz probe is 3–12 cm or 2–7 cm respectively. In order to image the placenta properly, the probe should not touch the cervix. Such contact results in a poor picture since the area of interest is outside the focal zone of the probe.

The case presented demonstrates that vaginal sonography can be safely used for accurate localization of the placenta. We are currently conducting a prospective study in which both magnetic resonance imaging and vaginal ultrasound are compared with abdominal ultrasound in assessing placenta praevia. We encourage obstetricians who are familiar with vaginal sonography to consider this technique, especially when the abdominal sonography is not satisfactory or when prolonged hospitalization is contemplated.

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Pelvic inflammatory disease caused by *Salmonella panama* and its treatment with ciprofloxacin. Case report

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Case report

A 40-year-old nulliparous woman, last menstrual period 8 October 1987, was admitted as an emergency on 15 October 1987. She gave a 1-week history of diffuse abdominal pain and flatulence. During the 12 h preceding admission she had intense colicky abdominal pain localized in the lower right quadrant with nausea and chills. At no time had she experienced diarrhoea. She had been on a holiday trip to France 1·5 weeks earlier.

On examination, she presented with tenderness in the lower right quadrant of the abdomen. She had a regular radial pulse of 100 beats/min, blood pressure of 130/80 mmHg, and axillary temperature of 37·3°C. Pelvic examination revealed tenderness in the right side. Laboratory investigations disclosed a white blood cell count of $8{\cdot}0 \times 10^9$/l, haematocrit 40%, pregnancy test negative, C-reactive protein (CRP) 78 mg/l, and erythrocyte sedimentation rate (ESR) 16 mm/h. Because acute appendicitis could not be excluded she underwent surgery. The appendix was normal, but bilateral salpingo-oophoritis was confirmed and there was pus in the cul-de-sac. Parenteral cefuroxime-metronidazole treatment was commenced. Bacteriological culture of abdominal pus yielded growth of a Gram-negative rod which was identified as *Salmonella panama* by standard microbiological methods (Kelly *et al.* 1985). The organism was susceptible to ampicillin, piperacillin, cefuroxime, chloramphenicol, tobramycin, cotrimoxazole, and ciprofloxacin by disk diffusion assay. No other aerobic or anaerobic bacteria or chlamydiae were found. The same species grew also from the stools. Cervical swabs for gonococcal growth and chlamydial antigen were negative. After the diagnosis of salmonellosis was confirmed (20 October) the antimicrobial treatment was changed to 500 mg ciprofloxacin twice daily. Before that, CRP had risen to 130 mg/l and ESR to 98 mm/h and the patient developed tubo-ovarian abscesses. At culdocentesis (26 October) 60 ml of pus with scanty growth of *S. panama* was obtained. During ciprofloxacin treatment the level of CRP fell to 46 mg/l (25 October) and to 20 mg/l (29 October). Pelvic ultrasound examination revealed a mass of 6–7 cm diameter behind the uterus and on 3 November culdocentesis was performed. Pus cultured for salmonellae and other bacteria exhibited no growth. Stool cultures for salmonella were negative on 22, 26 and 29 October. There was a rise in titre of antibodies against the non-specific phase of *S. paratyphi* H-antigen which is shared by *S. panama* (22 October, negative; 11 November, 400). Titres of antibodies against *Neisseria gonorrhoeae* antigen studied by enzyme immunoassay were negative; however, against *Chlamydia trachomatis* antigen a moderately high titre of 128 was seen by immunofluorescence.

After the last culdocentesis the patient's recovery was uneventful and she was discharged in good condition on 16 November 1987 when ciprofloxacin treatment was stopped. CRP was normal (<10 mg/l), ESR 33 mm/h, pelvic ultrasound revealed a normal uterus and left adnexa and a 2·5 cm cyst in the right side. There were no adverse effects due to ciprofloxacin treatment except a slight elevation in serum levels of aminotransferases and alkaline phosphatase.

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Outpatient examination (4 December) showed a slightly enlarged right ovary, CRP<10 mg/l, and ESR of 10 mm/h. On further outpatient examination (5 January 1988) the ovary was still enlarged, CRP <10 mg/l, ESR 4 mm/h and stool culture for salmonellae negative. Because of an enlarged right ovary a laparotomy was performed on 16 February. Bilateral sactosalpinx and an enlarged right ovary with a 5-cm endometriotic cyst was found. The left ovary was normal. The uterus, both fallopian tubes and right ovary were removed. Bacterial cultures from the peritoneal cavity and fluid from fallopian tubes yielded no growth.

Discussion

Infections by Gram-negative bacteria of the genus *Salmonella* may be classified as typhoid fever, caused by *S. typhi,* and as the non-typhoidal salmonellosis, the latter ranking among the most important infectious diseases. Humans are infected by the ingestion of contaminated food or drink either of domestic origin or nowadays due to increasing tourism even more often during holidays abroad (Editorial 1987; Hornick 1983; Kelly *et al.* 1985). Gastroenteritis, the most typical symptom, may be accompanied by bacteraemia even with the non-typhoidal *Salmonella* spp.; focal manifestations involving bone, joints, lung, heart and the urinary tract, however, occur more rarely (Hornick 1983).

Salpingo-oophoritis is typically caused by *Neisseria gonorrhoeae, Chlamydia trachomatis,* enterobacteria, anaerobic bacteria, *Ureaplasma* sp. or *Mycoplasma* sp. Rare causes include *Haemophilus influenzae* and *Actinomyces* sp. Homosexual as well as anal- and oral-genital practices have allowed a number of gastrointestinal and systemic pathogens, among them salmonellae, to be considered as aetiological agents of sexually transmitted diseases (Finegold & Baron 1986). In addition, salmonellae possess a known tendency to localize to sites of pre-existing disease (Hornick 1983). In the female genital tract this may take place by the ascending route, through direct contact with the inflammed bowel wall or by haematogenous spread.

The pathogenicity to man of *S. typhi* among salmonellae is well known and there are also reports of localized infection caused by this organism in the female genital tract, pregnancy being a predisposing factor (Duff & Engelsgjerd 1983; Duncan *et al.* 1981; Nuttall *et al.* 1980). The other 'minor salmonellae' may in connection with gastroenteritis infect places of low resistance, e.g. post-traumatic subdural haematoma (Boles *et al.* 1983) or prothetic and even native heart valves (Hanger *et al.* 1985). In gynaecological patients the targets have especially been endometriotic ovaries, i.e. infection by *S. brandenburg* (Magliulo *et al.* 1982) and *S. stanley* (Ghose *et al.* 1986), or a dermoid ovarian cyst, i.e. by *S. paratyphi A* (Michelet *et al.* 1985). In addition, *S. enteritidis* has caused bilateral tubo-ovarian abscesses in a patient with the sickle cell trait as a predisposing factor (Saltzman *et al.* 1984).

The patient described here presented with symptoms of gastroenteritis and appendicitis after a holiday trip to France. During surgery, however, the cause of abdominal pain was discovered to be acute salpingitis. *S. panama* was grown from pus evacuated from the peritoneal cavity as well as from stools. It is noteworthy that our patient had endometriosis in the right ovary which may predispose to salmonellal tubo-ovarian abscess. She had no previous history of other inflammatory disease in the genital tract, but a moderately high immunofluorescence antibody titre against *C. trachomatis* antigens was found which may indicate simultaneous deep chlamydial infection.

Ciprofloxacin, one of the new 4-quinolone antibacterial agents (Neu 1987) was used as medication once the salmonellal aetiology of infection was determined. At present it is considered as the most effective antimicrobial for eradication of salmonellae from the stools (Pichler *et al.* 1987) and good penetration to female genital tissues has been found (Dalhoff & Weuta 1987). Accordingly, stool cultures became negative and no salmonellae were grown from pus aspirated by culdocentesis after 14 days of treatment with ciprofloxacin.

We suggest that ciprofloxacin is effective in the treatment of pelvic inflammatory disease caused by salmonellae. Also, radical surgery which has been necessary in previously published cases can be avoided. This has great potential importance in patients of childbearing age.

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CORRESPONDENCE

Commentary. Broken bones—a gynaecological problem

Dear Sir,

Your commentary by Dr Purdie [*Br J Obstet Gynaecol* (1988) **95**, 737–739] presents an overwhelming case for the prevention of menopausal osteoporosis by hormone replacement therapy. Assuming only a quarter of women in the menopausal age range desire or require hormone therapy the health service has to provide facilities to counsel, treat and follow up $2{\cdot}5\times10^6$ women annually.

It is essential to combine the efforts of hospital gynaecologists and general practitioners in catering for the needs of this large section of the population. However, a third outlet for the provision of such services exists in the community family planning/womens' health services. Community clinics may be the ideal setting for providing a preventive service for essentially healthy women. The ideal is for this identifiable body of health professionals to be primarily responsible for the care of the 'mature woman' and to provide the flexible link between primary care and hospital gynaecology, releasing valuable time and medical skills for both.

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Cervical stenosis after cone biopsy during post-pregnancy amenorrhoea

Dear Sir,

We read with interest the paper on cervical stenosis after cone biopsy during post-pregnancy amenorrhoea by Moncrieff & Steel [*Br J Obstet Gynaecol* (1988) **95**, 628–629]. We have seen a similar case of stenosis of the uterine cervix following cone biopsy which resulted in amenorrhoea and infertility. In fact, dilatation and curettage was impossible under anaesthesia because only a dimple could be seen at the site of the previous os. To treat our patient a CO_2 laser was used to fashion a new cervical os. This was done as an outpatient procedure, aiming the CO_2 laser at the dimple and waiting until mucus and discharge were expressed. A laser cone was then fashioned without any difficulty. Following this treatment the cervical canal has remained patent although so far there is no report of a pregnancy.

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A study comparing transcervical with transabdominal chorionic villus sampling (CVS)

Dear Sir,

Mackenzie *et al.* [*Br J Obstet Gynaecol* (1988) **95**, 75–78] investigated the size of the chorionic villus samples obtained by the transcervical route and the transabdominal route. They suggested that, although some investigators had obtained specimens weighing >30 mg with the transabdominal method (Smidt-Jensen *et al.* 1986), larger amounts of material were obtained with the transcervical technique. Because of this finding, they preferred the transcervical method when enzyme and DNA analysis was required (Upadyaya *et al.* 1984). In our opinion there is no correlation between the amount of tissue collected and successful direct chromosomal analysis. Quite the opposite was observed in our study involving 330 samples of chorionic villi obtained by the transcervical approach, since we encountered the greatest difficulty in determining the karyotype with larger biopsy specimens (>30 mg). Rather than quantity, we believe that the quality of villi collected is the most important criterion. Indeed, the 64 specimens we obtained by the transabdominal approach (24 during the first trimester and 40 during the second and third trimesters of pregnancy) always weighed <5 mg and enabled determination of the karyotype each time by the direct method (Horovitz *et al.* 1988; Saura *et al.* 1988). Transabdominal sampling made it possible to collect 'good quality' villi from the middle of the chorionic plate. The mitotic index of these tissues was high. Samples obtained by the transcervical method in some cases consisted of peripheral villi, referred to as involuted without budding, and with a low mitotic index.

In addition, the transabdominal method decreases the risk of bacterial infection, and the frequency of fetal loss appears to be lower than when the transcervical method is employed, being 2·4% and 3·5%, respectively, in the series compiled by Laird Jackson (*Chorionic Villus Sampling Newsletter* 1988). The small amount of tissue which characterizes the transabdominal method should not be a factor limiting the use of this approach in the prenatal diagnosis of chromosomal aberrations.

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Authors' reply

Dear Sir,

We would like to thank Dr Saura and his colleagues for their interest in our paper comparing transabdominal with transcervical chorionic villus sampling (CVS). It was interesting to note that their diagnostic experience of smaller villus samples obtained by the transabdominal route agreed with the findings in our paper. A minimum of at least 20 mg of villi is usually requested by laboratories performing enzymatic or DNA analysis and this may be more difficult to obtain with the transabdominal approach. Their experience of karyotype analysis from villi is confirmed by our own experience and we would agree that quality of villi is important and not quantity, but it would seem to be obvious that the more villi that one obtains the greater the likelihood of obtaining good villi for any one sample. It is possible to avoid villi from the periphery by placing the cannula tip further within the placenta as assessed by real-time ultrasound. In our opinion it is pointless quoting miscarriage rates associated with transabdominal compared with transcervical CVS, as no quoted series has been a controlled study and miscarriage rates after transcervical CVS in some series are as low as 1·9% and after transabdominal sampling from 0·7 to 4·8% (L. Jackson, *CVS Newsletter,* August 1988). Until the results of controlled clinical trials examining transabdominal and transcervical CVS are available, it will be impossible to quote a true excess miscarriage rate from either of these procedures.

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BOOK REVIEWS

The Obstetric Forceps: A Short History and Descriptive Catalogue of the Forceps in the Museum of the Royal College of Obstetricians and Gynaecologists by Bryan M. Hibbard. Available from the Royal College of Obstetricians and Gynaecologists, 27 Sussex Place, Regent's Park, London NW1 4RG, 66 pages with figures and tables, £2.00

Obstetric forceps have saved more lives in the last 300 years than any other surgical instrument, except perhaps the tourniquet. For delivering live babies their use may have started with the Chamberlain family whose business practices now cause a shudder, but when judged against the rest of society in the 17th century, they made as much sense as do other economically based sets of morals today in the Thatcher era. Modifications of forceps instruments proliferated and it almost became a point of honour for obstetricians to design their own instrument. Having invented it, they would go on using it and, if in a position of influence, teach its use to others. Now, in a more rational age, we use few types of instrument; probably most departments in the Western world work with some variation of a short forceps (Wrigley's), a medium length forceps (Anderson's) and a straight forceps (Kjelland's).

A great collection of forceps is now housed at the Royal College of Obstetricians and Gynaecologists, much of it being due to the interest and activities of the late John Harrington. Thanks to a grant from the Wellcome Trust, the Museum at the College House has now been revived and an excellent display of forceps may be seen. This display was arranged by Professor Bryan Hibbard with help from the Wellcome Museum of the History of Medicine; this small book is best read in association with the Museum exhibition. It certainly makes a couple of hours spent at that Museum much more interesting and your reviewer thoroughly enjoyed learning new facts about the mechanics of obstetrics.

To those who cannot get to the Museum, the booklet is still good value for it contains a most readable account of development of the forceps, indicating why variations were considered necessary and what benefits they brought. Professor Hibbard has done a valuable service to obstetrics in providing this short but full account of the evolution of the obstetric forceps. For the sake of the many RCOG members overseas and obstetricians who are not fellows and members of the College, the Royal College may consider producing slides of illustrations of specimen forceps or even a small pouch at the back of this volume containing slides of the most important instruments indicative of the changes in evolution.

This volume is thoroughly recommended to all who practise obstetrics and have a curiosity about the instruments they use every day.

Geoffrey Chamberlain

Voiding Function and Dysfunction: A Logical and Practical Approach by Alan J. Wein & David M. Barrett. Year Book Medical Publishers, Inc., New York, 1988, 371 pages with figures and tables, £28.50

This soft-backed book, written by two well-known North American authorities, is presented in two sections. The first part is devoted to the anatomy, physiology and pharmacology of the lower urinary tract. There is a long section describing the nervous control of micturition. Where views expressed in the literature are at variance both sides are fairly quoted to give the reader a balanced overview. This first section of the book ends with a useful description of normal bladder filling/storage and emptying.

The second part relates to voiding dysfunction. There is a short chapter on neurological evaluation followed by a helpful description of the commonly performed urodynamic tests and their application. I found the classification of voiding dysfunction somewhat confusing as no less than seven different systems are quoted. Treatment of voiding dysfunction is covered thoroughly, considering the overall size of the text, and all the common types of therapy are mentioned. At the end of the book a few special situations, such as neurological and paediatric voiding dysfunction, are dealt with in more detail.

Although the book is written in a style which I did not always find easy to follow, I think it will prove particularly useful to young doctors, especially those in training, who have an interest in lower urinary tract problems, as it does include a great deal of basic material. Its most useful aspect to me is its exhaustive, well-balanced bibliography which unfortunately only includes a couple of 1986 references and none beyond.

It is a shame that the binding is such poor quality that it came apart before I had finished reading the book, but I am glad to see that the price is reasonable and think that the book will find a place on the bookshelves of many interested practitioners who currently have a poor understanding of normal and abnormal voiding.

Linda Cardozo

An 'Epidemic' of Adolescent Pregnancy? Some Historical and Policy Considerations edited by Maris A. Vinovskis. Oxford University Press, Oxford, 1988, 284 pages with figures and tables, £22.50

The conflict between private and public attitudes to sexual morality makes the subject an uncomfortable one for political debate. The first part of this book traces the history of adolescent pregnancy in the USA from early colonial days when attitudes were largely those of the contemporary British. A pregnant girl was expected to marry, not only to make her respectable, but to provide a breadwinner for the family. Since those days, social attitudes have radically changed, especially during the 1960s. Young pregnant girls no longer accept either marriage or adoption as an acceptable solution to their problem, preferring abortion or single parenthood. The increased number of young unmarried mothers, unable to support themselves and deprived of education, became the focus of a good deal of public concern, and in 1978 the Carter Administration in the USA introduced the *Adolescent Health Services and Pregnancy Prevention and Care Act* and set up the Office of Adolescent Pregnancy Programs. With the involvement of public funds morality became fair game for political rhetoric.

The author examines the nature of the debates in the Senate over the provision of contraception services under the Carter and Reagan administrations. One notable argument occurred in 1982 over the question of parental consent for sexually active girls below the age of 16, and British readers will note the close analogy with the Gillick controversy.

There are some interesting comments about the role of the father in adolescent pregnancy, and a disappointingly brief account of a survey of teenagers. The book is mainly about American politics, and although there are obvious parallels with Britain, it is not of direct interest to those concerned with the medical or sociological aspects of pregnancy.

S. L. Barron

The Menopause: Comprehensive Management. Second edition edited by Bernard A. Eskin. Macmillan Publishing Company, New York, 1988, 350 pages with figures and tables, £32.50

This is an important book about an important subject. The menopause affects so many different systems that it is almost impossible for the practising doctor to keep abreast in all of them. Now here is a chance to catch up on recent research.

Fink explains patients' anxieties and ambivalence in the face of a male-dominated medical profession and its vacillating attitude towards hormone replacement therapy (HRT). Eskin writes on the menopause and ageing, and an up-to-date account is given of pathology, osteoporosis and urological problems. Nutrition and hormonal metabolism are described and Leiblum and Bacham report their study showing that continuing sexual activity is protective against vaginal atrophy.

The only disappointing chapters are those on HRT and this merely shows that by the time a textbook is published some sections are already out of date. British gynaecologists would not agree that the course of progestogens in HRT should be only '7–10 days'. Transdermal oestrogen does not need to be cyclic and if given to women with a uterus should be supplemented with progestogen. Vaginal cream is absorbed and users should be warned that it may cause postmenopausal bleeding. Perhaps more prominence could be given to the need for mammography in long-term users of HRT, and the chapter on cancer should state that previous users of oestrogen continue to have an increased risk of endometrial cancer for many years. Clinical indications for HRT should include a list of the risk factors for osteoporosis.

However, this is a useful book, well produced with generous margins and clear diagrams, and it will be appreciated by doctors who are working in this field.

Jean Coope

Foundations of Obstetric Anaesthesia edited by Barbara Morgan. Farrand Press, London, 1987, 309 pages with figures and tables, £19.50

Barbara Morgan is one of the leading figures in obstetric anaesthesia and she is well placed to produce a book to stand with the two texts which currently dominate the teaching of obstetric anaesthesia in the UK. Many obstetricians will know her as a contributor, on the subject of anaesthetic facilities, to the National Birthday Trust Report on Facilities at the Place of Birth. She is also widely known in connection with the popular and successful courses at Queen Charlotte's Maternity Hospital. Several of the contributors to the book are her colleagues at Queen Charlotte's and the remainder, except for some well-known names from Oxford and Glasgow, are drawn from other London teaching hospitals. Any hint of nepotism can, however, be quickly dispelled by the realization that it would be very difficult for an editor to find more authoritative writers than Michael de Swiet on pregnancy and cardiovascular disease, Elizabeth Letsky on haemostasis in pregnancy, Gillian Hanson on shock in obstetric patients, or Felicity Reynolds on placental transfer. The cornerstones of the work are the didactic accounts of analgesia and anaesthesia for vaginal delivery and caesarean section, together with the anatomy and physiology, complications and side-effects of the available methods. For anaesthetists who want to be involved in childbirth and its complications in a multidisciplinary approach to perinatology there are also sound introductions to the management of labour, assessment of fetal well-being, the effect of drugs on the newborn baby and aspects of neonatal intensive care. Each chapter begins with an enumerated plan of headings and subheadings which contributes to a reader-friendly product. The only exception to this format is the capitivating historical review of regional analgesia in obstetrics by Andrew Doughty. This is an attractive book in appearance as well as content and I expect that it will, as the name implies, become part of the foundations of obstetric anaesthesia.

R. P. Husemeyer

Pathology of Infertility: Clinical Correlations in the Male and Female edited by Bernard Gondos & Daniel H. Riddick. Thieme Medical Publishers, Inc., New York, 1987, 388 pages with figures and tables, DM 189

Ten years ago, before assisted reproduction, there was little doubt that the way forward in the infertility field was to gain a better understanding of normal reproduction and the abnormal function in couples with fertility problems. Methods of assisted reproduction, particularly IVF and GIFT, have changed the horizon for clinicians and patients. These differ from more orthodox therapies by providing relief from the symptom, in this case infertility, without correcting the underlying aberration causing the infertility. This is analogous to many areas of medical practice where therapies are directed at alleviating symptoms or correcting physical signs Where the analogy is incomplete is that such therapies in asthma, hypertension, heart failure, etc. have high efficacy, are usually not invasive, are freely available on the NHS and do not create ethical and moral dilemmas for patients. The same cannot be said for assisted reproduction. If these and other related issues are ever solved then perhaps the need to gain a deeper understanding of infertility processes could become a matter of academic interest as far as clinicians and patients are concerned. At present that is definitely not the case so books like the present example are to be welcomed.

The title *Pathology of Infertility* implies that this is principally a work of interest to pathologists but my impression is that it is written for practising infertility clinicians. Clinicians require books which present an up-to-date account of reproductive pathophysiology and the interpretation of investigations of that function. This work meets that need.

The 30 American contributors come from obstetrics and gynaecology and pathology departments across the USA and give an integrated approach to current knowledge Approximately two-thirds of the book address female aspects of infertility and one-third looks at the male.

There are many ways to organize the material.

The editors have opted for a layout based on anatomical areas, e.g. cervix, uterus, etc. with some broader-based contributions, e.g. immunology of infertility. The contributions are mostly well illustrated and the page layout is easy on the eye but none of the histological illustrations is in colour. Most chapters are 15–20 pages so can be read at a couple of sittings.

The ovary and disorders affecting ovulation have tended to dominate the infertility literature. I was pleased to see that this text has taken a broad-based look at fertility with only five of the 21 chapters dealing with the ovary and ovulation. The range of chapters on female problems includes 'Inflammatory and traumatic conditions of the cervix' (Moghissi); 'Immunologic abnormalities of the female tract' (Bronson); 'Congenital abnormalities of the uterus' (Jones). The extent of referencing varies with the contributors, with many chapters constituting review monographs with 100–200 references. I did note with interest that the extensively referenced chapter on polycystic ovarian syndrome, which included references up to 1986, made no mention of the British work on ultrasonic diagnosis and assessment of polycystic ovarian morphology. This omission can possibly be explained, but not excused, on the basis of the American origin of the book.

This book, which is expensive, would be a useful addition to the library shelf of teams practising in clinical infertility, particularly because of some of the less usual topics addressed, but at a time when so many books on infertility are being published I suspect that many such specialists will forego obtaining a personal copy.

David H. Barlow

Books received some of which may be reviewed at a later date

Twinning and Twins edited by Ian MacGillivray, Doris M. Campbell & Barbara Thompson. John Wiley & Sons, Chichester, 1988, 321 pages with figures and tables, £52.50

Genitourinary Trauma edited by Alexander S. Cass. Blackwell Scientific Publications, Boston, Oxford, 1988, 298 pages with figures and tables, £45.00

Obstetric and Gynecologic Physical Therapy (Clinics in Physical Therapy Vol. 20) edited by Elaine Wilder. Churchill Livingstone, Edinburgh, New York, 225 pages with figures and tables, £22.50

A Manual of Normal Neonatal Care by N. R. C. Roberton. Edward Arnold, London, 1988, 240 pages with figures and tables, £7.95

Multiple Sclerosis: Exploring Sickness and Health by Elizabeth Forsythe. Faber & Faber Ltd, London, 147 pages, £4.95

Neale's Yard Natural Remedies by Susan Curtis, Romy Fraser & Irene Kohler. Arkana Penguin Books Ltd, London, 1988, 182 pages, £5.99

Atlas of Obstetrical Ultrasound by Carol B. Benson, Thomas B. Jones, Marcia J. Lavery & Lawrence D. Platt. J. Lippincott Company, Philadelphia, London, 1988, 304 pages, £35.00

Oxford Reviews of Reproductive Biology, Vol. 10 1988 edited by J. R. Clarke. Oxford University Press, Oxford, 1988, 519 pages with figures and tables, £55.00

British Medical Bulletin Vol. 44 No. 4 1988 The Very Immature Infant: Less Than 28 Weeks Gestation Scientific editors A. Whitelaw & R. W. I. Cooke. Published for the British Council by Churchill Livingstone, Edinburgh, 1988, single copies £25.00 (UK) or £31.50 (overseas)

Reports and Symposia

Gynaecological Pathology Report of the Joint Working Party of the Royal College of Obstetricians and Gynaecologists and The Royal College of Pathologists. Available from the Royal College of Obstetricians and Gynaecologists, 27 Sussex Place, Regent's Park, London NW1 4RG, £2.00

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COMMENTARY

Human immunodeficiency virus infection in women

Two papers concerning the human immunodeficiency virus (HIV) appear in this issue of the Journal. One by Howard *et al.* (p. 135) discusses screening for HIV in antenatal and genitourinary clinic populations and the other by Howard-Gardiner *et al.* (p. 140) describes paediatric HIV infection.

The first evidence for heterosexual transmission of HIV was reported by Harris *et al.* (1983). Since then, studies from Africa have confirmed that heterosexual transmission is the leading route of HIV infection worldwide. In Europe and the USA the majority of seropositive women have been infected by intravenous drug abuse but heterosexual transmission is becoming increasingly important (Starcher *et al.* 1988). In the British Isles the problem is still on a relatively small scale with 524 HIV-seropositive women (in England and Wales), of whom 61 have acquired immunodeficiency syndrome (AIDS), reported to the CDSC up until the end of September 1988. Many, of course, must remain unreported or undetected.

The risks of acquiring HIV in heterosexual couples in long-term relationships is uncertain, with widely differing rates being reported. The cumulative rate of infection has been reported to be significantly higher among the female partners of infected intravenous drug abusers or men from countries in central Africa, than among the female partners of bisexual men, or blood product recipients (CDC 1986). Attempts are being made to define factors which increase heterosexual transmission and it is clear that there is some correlation with the number of sexual partners (Fischl *et al.* 1988*a*). The presence of genital ulceration caused by syphilis, herpes simplex or other agents is associated with an increased risk of HIV infection (Fischl *et al.* 1988*b*). It has been suggested that damage to the genital skin or mucosa by these infections may facilitate transmission. Vaginal intercourse is responsible for most cases of heterosexual transmission, although receptive anal intercourse may increase the risk of infection in women (De Vincenzi 1988); the risk from orogenital contact is unknown. The probability of acquiring HIV also increases with advancing clinical disease and falling CD4 lymphocytes in the infected partner (Piot *et al.* 1988; Fischl *et al.* 1988*b*).

The natural history of HIV infection in women is less well studied than that in the male population, but there is no evidence as yet to suggest that infection in women behaves differently. The clinical manifestations of AIDS in women are very similar to those reported in men. Kaposi's sarcoma is the exception, occurring in only 1% of females with AIDS as opposed to 3% of heterosexual and 23% of homosexual males (Saltzman *et al.* 1988).

The epidemiological evidence now indicates that HIV infection represents a relentlessly progressive immunological disorder. Prospective studies in homosexual men, haemophiliacs and blood transfusion recipients suggest that progression from infection to AIDS is slow, taking an average of 8–10 years in homosexual men (Moss *et al.* 1988; Lui *et al.* 1988). Potentially all those infected may develop AIDS and all patients should, thus, be under clinical surveillance. Much attention has focused on markers to predict disease advancement. Falling CD4 lymphocyte counts are widely measured to predict clinical disease but there is wide individual variation (Moss *et al.* 1988). The presence of HIV p24 core antigen is used but is insensitive (Allain *et al.* 1987; Osmand *et al.* 1988). Increased serum concentration of B2 microglobulin (Moss *et al.* 1988) or neopterin (Fuchs *et al.* 1988) have been proposed as predictors of advancing disease, and may prove to be more powerful tools in the monitoring of patients. At present, monitoring of the above factors in combination probably provides the most useful information on disease progression in an individual patient.

Despite early reports to the contrary, it now seems that pregnancy does not have a detrimental effect on an individual woman's infection (MacCallum *et al.* 1988), and further evidence for this is provided in this Journal by Howard-Gardiner *et al.* In normal HIV-negative women, CD4 counts and proportions fall to a nadir at about 7 months gestation and rise towards term, to remain elevated until approximately 9 months postpartum. In HIV-seropositive women, CD4 levels parallel the normal changes but at a lower level (Biggar *et al.* 1988).

Pregnancy outcome *per se* appears not to be affected by HIV infection in seropositive women. Multicentre European studies of groups composed largely of intravenous drug abusers suggest that there is little additional risk of low birthweight and prematurity in children of HIV-infected women when compared with HIV-seronegative intravenous drug abusers (The European Collaborative Study 1988; Italian Multicentre Study 1988).

There is now clear evidence of HIV transmission to the fetus during pregnancy. Infection during early pregnancy is suggested by the distinct HIV embryopathy that has been described (Wiznia *et al.* 1988). Apart from this rare sequela, virus antigen has been detected in the thymus of a baby born preterm by caesarean section to a woman with AIDS where there was no contact of mother with baby after birth (Lapointe *et al.* 1985). Virus has also been found in fetuses obtained at therapeutic abortion. In a recent study, two of six fetuses examined had p24 antigen present, clearly indicating transplacental infection (Peutherer *et al.* 1988).

Theoretically, HIV infection may occur during delivery. Virus has been isolated from cervical secretions, and thus the infant may be inoculated with virus during delivery, but there is, as yet, no evidence on which to recommend caesarean section as a means of reducing vertical transmission.

The virus has been isolated from the non-cellular fraction of breast milk (Thiry *et al.* 1985), and transmission of HIV from mother to child has been reported in lactating mothers infected postpartum by blood transfusion (Ziegler *et al.* 1985; Weinbreck *et al.* 1988). Seropositive women in the UK should be advised not to breast-feed, as safe alternative methods of feeding are available. In addition they should not contribute to milk banks.

Transmission of HIV through blood transfusion in newborn infants has been shown to result in a high incidence of infection (Saulsbury *et al.* 1987). With the screening of blood donors for HIV antibody, and the heat treatment of clotting factor concentrates, infection from blood products has now been almost entirely abolished.

Diagnosis of HIV infection in infants is difficult. At birth all babies of seropositive mothers are HIV antibody positive because of passively acquired antibody, which may remain for many months postpartum. Persistence of antibody beyond 15 months is assumed to indicate transmission of infection to the infant, but some infected infants, like adults, may become antibody negative as AIDS develops. Diagnosis is more reliably made on the isolation of virus; newer techniques such as the detection of proviral DNA by polymerase chain reaction have yet to be fully assessed (Ou *et al.* 1988).

Thus, the risk to children of becoming infected during pregnancy is unknown. The European Collaborative Study (1988) reported that of 100 babies born to HIV-seropositive mothers and followed for at least 15 months, or until death from AIDS or AIDS-related complex, 24 (24%) were presumed to be infected with HIV. This may, however, be an underestimate of the number infected for the reasons outlined above. A preliminary report from this study suggested an association between clinical symptoms of HIV infection in the mother and infection in infants (Mok *et al.* 1987). However, with the accumulation of more data this association was no longer apparent. Only 5% of mothers in this study had advanced disease; a larger group of symptomatic patients would need to be studied in order to assess effect of disease status on HIV transmission. A similar transmission rate of 33% is reported in the Italian Multicentre Study (1988) of 89 children followed from birth to at least 15 months of age.

What advice should be offered to seropositive women or patients with AIDS, pregnant or contemplating pregnancy? A woman with AIDS has a poor prognosis and possibly a high risk of transmitting infection to her infant should she become pregnant. These women should be counselled and termination recommended. An asymptomatic seropositive woman considering pregnancy should be advised to delay pregnancy until more is known about the risks of transmission to the fetus and the natural history of her HIV infection. Those already pregnant should have the available information explained to them and should be offered termination.

Attempts need to be made to identify high-risk women before they become pregnant, both in general practice and in family planning clinics. Patients can then be counselled, and tested when appropriate. In the antenatal clinic, testing should be available for all women who request it, and be offered to those with risk factors. For this to be effective it is essential that all obstetric and midwifery staff are trained in identifying high-risk patients.

The ethical implications of antenatal screening are considerable (Howard *et al.* p. 135). It is inadequate to opt for routine screening by consent if 35%, who may be those at high risk, refuse to be tested. Such a policy is wasteful of time and resources and produces worthless epidemiological information. The present policy in the UK and the USA is not to offer routine screening, and is probably correct. Compulsory screening would clarify the epidemiology of the disease but the contemporary ethical view would find this unacceptable, as the individual's rights would be violated. Strictly anonymous testing appears to be a compromise although one doubts the clinical wisdom of being unable to identify and counsel a pregnant woman when the prognosis for her and her infant is so poor.

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Reducing late abortions

A year ago a meeting was organized by the Birth Control Trust on reducing late abortions, and a report of the proceedings has now been published (Birth Control Trust 1988). Referral and assessment for abortion takes longer within the National Health Service (NHS) than in the private and charitable sectors. The NHS carries out only 21% of all its abortions before the 9th week as against 44% in the private sector. The NHS is peculiarly reluctant to perform second-trimester abortion when the indications are social factors threatening mental health. The report deals with many specific issues including the need for better provision of early pregnancy testing in general practice and in community clinics, the early detection of fetal abnormality and the very great regional variations in the provision of abortion within the NHS. It describes how the Service can in fact provide good abortion facilities and gives examples from several centres in England. Each contribution demonstrates how improvements could be made and the decision-making process speeded up. All who are seriously interested in abortion should study this report.

There is a great difference between abortion performed early in pregnancy and when there has been delay. Firstly the woman's feelings change. Initially she knows only that her period is late, then she realizes that she is pregnant and only later comes to feel that she is going to have a baby. This is why, until modern times, abortion was not regarded as a crime up to the time when the woman felt quickening. Secondly, as regards the actual operative procedures, abortion using suction is a simple and safe procedure best carried out on an outpatient basis within the first 12 weeks of pregnancy. Even within the first trimester, technical difficulty and therefore complications increase sharply with fetal age. In the report Wendy Savage states that the complication rate is increased by 60% by delaying abortion from 8 to 10 weeks. The ill-effects of delay become even worse as the fetal age increases. Second-trimester abortion involves either medical induction allowing the conscious woman to abort or considerable dilatation of the cervix and evacuation of the uterus, a technique requiring considerable expertise. Late abortion is always psychologically traumatic to the woman and to her medical and nursing attendants because the fetus is now recognizably human.

Early abortion uses fewer health resources, involves less time off work or away from the family and is far more acceptable to the woman. Clearly all abortions should be done as early as possible and the UK has an exceptionally bad record in this respect (Henshaw 1986). There are now many countries, such as France and Denmark, with laws allowing early abortion by agreement between patient and doctor but imposing restrictions when the pregnancy is more advanced. In all these countries the average fetal age at abortion is lower than in Britain. In those countries which control their birth rate primarily by abortion rather than contraception, for example Russia, Japan and China, anything over 8 weeks would be regarded as a late abortion. Sometimes delay is unavoidable: amniocentesis to detect chromosomal abnormality is not currently feasible before the 15th or 16th week and the results are commonly available 3 weeks later. Similarly the use of ultrasound to detect abnormalities of the heart or brain has to wait until 18–20 weeks and in some cases until an even later gestation.

When considering the basic causes of delay, the attitude and behaviour of the woman herself is important. For her the unwanted pregnancy is a new, highly emotional and confusing experience. Her attitude towards the pregnancy may be ambivalent and she may be uncertain of her consort's reaction. Very young women may take a particularly long time to come to a decision. If the woman chooses abortion she still may not realize the need for urgent discussion with her general practitioner. Except for occasional articles in women's magazines there has been no national attempt to educate women on the management of unwanted pregnancy. A further cause of delay is the late diagnosis of pregnancy in women with irregular menstrual cycles. This is a particular problem in the early teens, premenopausally and following a pregnancy: all situations where the woman may well be subject to hormonally induced emotional instability.

Much responsibility for delay lies with the medical profession. The reasons are complex. Abortion is not a normal medical problem. The woman does not present with symptoms and signs in need of diagnosis and treatment. Usually she knows the diagnosis and has already decided upon the treatment she wants. Doctors are not trained for this situation and may not function well in the advisory role which it forces upon them. That the medical profession is failing to cope is shown by the fact that the NHS performs fewer than half of all those abortions carried out in women who are UK residents. A woman seeking abortion must first consult her general practitioner, and time is frequently lost in obtaining a pregnancy test and then by insistence upon one or more counselling sessions before referral to a gynaecologist. It has been shown that there are frequently long delays while the woman waits for an appointment. The gynaecologist may have no special arrangements for seeing abortion cases quickly and may be able (or willing) to see very few such cases. Even when abortion is agreed there is likely to be further delay before a bed and operating time can be found. The gynaecologist has to take into account the needs of other women with urgent gynaecological problems and, unless special arrangements exist for day-stay abortion by less highly qualified staff, the competition for scarce resources inevitably leads to harmful delays.

Doctors are affected by the attitudes of society and of politicians towards abortion. Although opinion polls have repeatedly and consistently shown that the public supports liberal abortion, the media tend to portray abortion as shameful and as being used too much The implication is that the profession is not being strict enough and that abortion is too easy. The regulations formulated by the Department of Health are perceived by doctors as being restrictive and threatening. The two doctors who are required to certify the need for abortion have to complete forms which are legalistic with reminders that inaccurate completion will involve penalties. They are instructed to *print* their name, qualifications and address and to ring or erase several subsidiary questions as to when and where they saw (and whether they actually examined) the woman. The bureaucratic procedures required by the abortion regulations are intended to emphasize the serious nature of the procedure contemplated but they do in fact discourage rapid decision making. Many doctors feel that completing such forms for which, unlike almost all other required notifications, no fee is payable, links them with the woman and with the practitioner who actually performs the operation and will involve them in responsibility which they would prefer to avoid. This may explain why many general practitioners who do not have a religious objection to abortion still refuse to complete Certificate A, preferring to send the woman to a clinic outside the NHS which will provide two certifying doctors and so take away their responsibility. The Secretary of State for Health, by virtue of his responsibility for the abortion regulations, must accept a share of the blame for delays which occur within the NHS and therefore for the number of women who are forced to seek help from the private clinics.

How can we change these negative attitudes? For the pregnant women themselves there must be education. If women consulted their general practitioners early enough and all general practitioners were aware of the need for swift action, the whole process would be speeded up. More importantly the politicians in charge at the Department of Health should accept from the published statistics that every health service district has a need for a predictable annual number of abortions and should direct health authorities to make provision for the abortion needs of each district. Planned abortion facilities are extremely cost-effective in that they ensure that as many abortions as possible are performed very early in pregnancy when they require only outpatient facilities and are within the technical competence of relatively junior staff. In 1974 the Lane Committee recommended that general practitioners were ideally suited to the management and performance of early abortion and they are so used in some areas. Special abortion facilities ensure that the women are dealt with by staff who are both sympathetic and experienced and who are able to provide them with the information and counselling they need. Expert gynaecological supervision is necessary and full gynaecological back-up essential, but assessment, counselling and performance of day-care abortion can be provided, and indeed are best provided, by part-time staff with a special interest in the work. There will always be some late abortions and these will require the skills of the full gynaecological team but the proportion of late abortions will fall dramatically when better abortion facilities are provided.

Politicians who genuinely wish to minimize late abortion should consider altering the Abortion Act to remove the current restrictions upon early abortion and the bureaucratic overtones which cause delays whilst retaining the present regulations for later procedures.

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Transmission of human immunodeficiency virus by heterosexual contact with reference to antenatal screening

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Summary. Twenty-seven women all of childbearing age, eight of whom were pregnant, were identified as human immunodeficiency virus (HIV-1) antibody positive in the genitourinary medicine clinics of East Riverside up to March 1987. Of these 27 women 11 had acquired the virus by heterosexual contact. Between 1 March 1987 and 29 February 1988, all 1328 women attending the antenatal clinic were offered an HIV screening test, 982 accepted and the other 346 declined to be tested. Two of the 982 tested women were found to be HIV-1 antibody positive. Two other pregnant HIV-1-positive women were identified during this time, one was tested in the genitourinary medicine clinic and the other whilst an in-patient for drug withdrawal. All except one of the 12 HIV-1-antibody-positive pregnant women were in known high-risk groups. In addition up to March 1988, 32 heterosexual men were identified as HIV-1 antibody positive and 22 of these were intravenous drug abusers. If the present trend continues, more women will become infected, often unaware that they are at risk and this may not be detected unless HIV testing is offered to all pregnant women and widely accepted. Decisions on local policy should be based on the available estimates of prevalence of HIV infection in that community.

By 29 February 1988, 34 adult women with acquired immunodeficiency syndrome (AIDS) and 779 adult women positive for HIV-1 antibodies had been reported in the UK. These numbers are small but are undoubtedly increasing and women, most of whom are of childbearing age, now account for 2·5% of all AIDS cases reported in the UK and 9·3% of known seropositives (CDSC and CD (Scotland) Unit 1987).

Most HIV-antibody-positive women in Europe and the USA have been infected through intravenous drug abuse, but an increasing number are becoming infected through heterosexual transmission (Guinan & Hardy 1987) and this is now the most rapidly increasing group of AIDS cases reported in the USA (Curran 1987).

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We have attempted to assess the problem of heterosexual transmission of HIV, in particular in women of childbearing age, in two ways: first, by review of our HIV testing data in the genitourinary medicine clinics of East Riverside District, and second, by a prospective study offering screening to all antenatal patients, which was primarily instigated on grounds of patient care.

Subjects and methods

Over a 3-year period up to October 1987, 2800 of 31 650 women attending the genitourinary medicine clinics at St Stephen's and Westminster Hospitals were tested for HIV infection after counselling.

Between 1 March 1987 and 29 February 1988 all antenatal patients attending the Westminster and St Stephen's Hospitals were offered the HIV antibody test at the time of booking. This was usually HIV-1 antibody testing only, but six women, most of whom were from West Africa, were tested for antibodies to HIV-2, but all were negative. All patients were counselled by specially trained midwives and they were only tested if they gave consent. It was emphasized that refusal to have an antibody test would not affect the management of the pregnancy. Confidentiality was discussed and the patient's general practitioner was only informed of the result with the patient's consent. Blood was tested for HIV-1 antibody by enzyme-linked immunosorbent assay (ELISA; Wellcome) and all positive results were confirmed on a second sample by radioimmunoassay (RIA) by Dr P. Mortimer, Virus Reference Laboratory, Colindale. Patients who were negative for HIV antibody, but were considered to be in a high-risk category, were offered a repeat test at 22 weeks gestation and again late in pregnancy.

Results

Up to March 1987, 27 women who were all of childbearing age (between 23 and 40 years) were found to be HIV-1 antibody positive. Fifteen of these were intravenous drug abusers, one was a blood transfusion recipient and 11 had acquired the infection heterosexually; they are detailed in Table 1. Of these 11 women, only five had felt they were at risk and presented requesting HIV antibody testing. Two had presented when

Table 1. Characteristics of 19 women with HIV infection acquired by heterosexual contact

Date of diagnosis	Age at diagnosis (years)	Status at diagnosis	Country of origin	Risk factor
Before 1/3/87				
01/85	37	PGL	UK	Bisexual partner
05/86	23	AIDS	UK	Bisexual partner
10/86	24	Well	Uganda	African
12/86	27	AIDS	UK	Previous partner IVDA
12/86	23	Well	Uganda	African
12/86	22	PGL	Uganda	African
12/86	25	PGL	USA	Multiple partners
01/87	25	Well	Namibia	African
01/87	25	Well	UK	Bisexual partner
01/87	30	PGL	USA	Multiple partners
02/87	26	Well	UK	Partner IVDA
Since 1/3/87				
04/87	27	Well	UK	Partner ex IVDA
04/87	23	Well	Rwanda	African
06/87	30	Well	Uganda	African
07/87	21	Well	UK	HIV-positive heterosexual partner
09/87	23	Well	Middle East	African sexual contact
12/87	27	PGL	Uganda	African
01/88	25	PGL	Uganda	African
02/88	19	PGL	Uganda	African

IVDA, Intravenous drug abuser; PGL, persistent generalized lymphadenopathy.

unwell and four had been offered testing (at either the genitourinary medicine clinic or antenatal clinic) because they were thought to be at risk. Eight out of 27 HIV-positive women were pregnant and all came from acknowledged 'high-risk groups' (Table 2), being either African or intravenous drug abusers.

In the first 12 months (March 1987–February 1988) of the policy of offering HIV antibody screening to all patients at booking in the antenatal clinic, 1328 women were seen, but 346 women declined testing, as they did not feel that they or their partner were at risk.

Of the remaining 982 women; two were HIV-1 antibody positive. One was a 30-year-old Ugandan who was tested at 10 weeks gestation. She had been living in the UK since 1982 and had been advised by her general practitioner before conception that she was not at risk of HIV because she had lived in the UK for 5 years. Her partner had returned to Africa for a holiday in January 1987. His HIV antibody status is unknown as he has declined testing. The second HIV-positive woman was a 26-year-old Italian intravenous drug abuser who was 36 weeks pregnant at the time of testing. She was admitted for drug withdrawal and had a normal delivery at 38 weeks gestation.

Over the same 12-month period a further two pregnant HIV-antibody-positive women were identified but not through the antenatal clinic. One was a 21-year-old white woman of UK origin who presented at the genitourinary medicine clinic for advice when 6 weeks pregnant. She had had a positive HIV antibody test performed privately. Her partner had recently discovered he was HIV antibody positive when he decided to be tested after noticing swollen glands in his neck. He denied homosexual contact and intravenous drug abuse but admitted to multiple contacts with prostitutes in Italy and West Germany. The patient intended to terminate the pregnancy but she had a miscarriage at 8 weeks gestation. The other woman was a 23-year-old intravenous drug abuser from Ireland who presented at 28 weeks gestation when admitted for drug withdrawal. Her partner is also known to be HIV antibody positive and was an intravenous drug abuser.

In addition up to January 1988, 10 heterosexual men were found to be HIV-1 antibody positive. Four of these had had multiple contacts with prostitutes abroad, two had known seropositive partners, two were African and in two there was no obvious risk factor.

Discussion

Limited information about the prevalence of HIV infection in the heterosexual community can be obtained from the 10 men and 19 women found to be HIV antibody positive in the genitourinary medicine and antenatal clinics of East Riverside over the last 3 years and who had

Table 2. Characteristics of pregnant HIV-antibody-positive women

Date of diagnosis	Age at diagnosis (years)	Gestation at diagnosis (weeks)	Risk factor	Outcome of pregnancy
Before 1/3/87				
10/86	24	29	Ugandan	Normal delivery at term
10/86	29	10	IVDA	Termination of pregnancy
11/86	20	9	IVDA	Termination of pregnancy
12/86	23	40	Ugandan	Normal delivery at term
12/86	29	22	IVDA	Termination of pregnancy
12/86	30	—	IVDA	Ectopic pregnancy
01/87	25	32	IVDA	Normal delivery at term
01/87	26	14	Namibian	Normal delivery at term
Since 1/3/87				
06/87	30	10	Ugandan	Unknown, returned to Africa
07/87	21	6	HIV-positive heterosexual partner	Miscarriage
09/87	23	28	IVDA	Normal delivery at term
02/88	26	36	IVDA	Normal delivery at 38 weeks

acquired their infection through heterosexual contact. It is, however, striking that although we only saw one patient who acquired the virus heterosexually in 1985, there were 11 (five men and six women) in 1986 and 14 (four men and 10 women) in 1987. There were in addition 22 HIV-antibody-positive heterosexual males and 20 HIV-antibody-positive heterosexual females who were also intravenous drug abusers.

As the frequency of HIV infection in our health district is particularly high because of the large population of homosexual men, up to 16% of whom are bisexual (Winkelstein *el al.* 1986), intravenous drug abusers and African immigrants, we felt we should investigate the seroprevalence rate of HIV infection in women of childbearing age. This would best be achieved by anonymous screening but there has been considerable discussion in the literature about the ethics of such screening with strong opinions on both sides, although a recent communication by a number of experts is strongly in favour (Black *et al.* 1987)

The present policy in the UK is not to offer routine screening to antenatal patients (Report of the RCOG Subcommittee 1987) and this is also the policy in the USA (MMWR 1987). It is, however, suggested that all women of childbearing age with identifiable risks for HIV infection should be counselled and tested for HIV antibodies. We felt it would be more appropriate to offer testing to all antenatal patients in our district for three reasons. First, many women and their partners in our area are worried about the possibility of HIV infection because of the perceived high risk locally, and the reassurance provided by counselling and testing is of positive benefit. Second, we felt that introducing a system of selective testing in so-called 'high-risk groups' was invidious and more difficult to accept by those patients in the high-risk groups. Third, routine questioning in the antenatal clinic may fail to elicit a history of foreign travel or drug abuse by the woman or her partner.

One benefit of HIV screening in the antenatal clinic is that it allows pregnant women the opportunity to consider the possibility of termination. Unfortunately an informed decision is hampered by a lack of firm data. The perinatal transmission of HIV varies in different series from 0% to 91% (Stewart *et al.* 1985; Chiodo *et al.* 1986; Scott *et al.* 1985; Luzi *et al.* 1985) but most authorities feel that about 50% of the offspring will become infected. Furthermore, the risk to the mother is difficult to quantify. Initial retrospective studies, where mothers were identified because they had previously had an infected child, showed a high mortality from AIDS within a short period of follow-up (Scott *et al.* 1985), although prospective data may be more reassuring (Mok *et al.* 1987; Professor Pardi, personal communication). It is suggested that the risk of ARC/AIDS is higher in infants born to mothers who have AIDS symptoms during pregnancy (Mok *et al.* 1987). The risk of transmission may be higher in those women who have HIV antigenaemia, consequently the use of 3'-azido thymidine (AZT) (Burroughs-Wellcome) during pregnancy may need to be considered but is not recommended at present. AZT has not been found to be teratogenic in rats (McEvoy & McQuarrie 1987) and can protect fetal mice against retrovirus infections *in utero* without visible harm to the mice (Sharpe *et al.* 1987).

Other benefits of HIV screening include counselling patients about the advisability of future pregnancies and the possibility of contact tracing to enable other 'at-risk' individuals to be counselled and help reduce further transmission of the virus.

Universal HIV testing in pregnancy would serve also to reassure midwives. Large quantities of body fluids are handled in perinatal care and the virus has been isolated from amniotic fluid (Mundy *et al.* 1987). Although management protocols should be designed to prevent risk of exposure and possible infection with HIV in all deliveries, this may be difficult to achieve in practice.

The relatively high rate of refusal of the test in the antenatal clinic, 26%, is perhaps surprising although most refusals occurred in the last 6 months of the survey and coincided with staff changes in the midwifery department. There is no doubt that the attitude of the counsellor has a marked impact on the patient's decision whether or not to agree to be tested for HIV antibodies. All the 346 women who declined the test said that they had no reason whatsoever to need this test and some even had strong negative feelings. However, most of the other patients accepted the test without question and many were under the impression that it was, and should be, a routine examination during pregnancy.

Our prevalence figures for the first 12 months of this prospective survey are encouragingly low but we would not expect to see much HIV seropositivity at this stage in the community, even if in the future we are faced by a heterosexual epidemic of HIV-infection. So far all the HIV-positive women we have identified in the antenatal clinic would have been detected if HIV testing had been offered only to 'high-risk groups'. However, we have seen several other women of childbearing age whose HIV status would not have been suspected from a routine clinical history obtained in an antenatal clinic. Therefore we intend to continue our present policy of counselling and offering the test to all pregnant women at booking as we believe it to be appropriate on clinical grounds.

Of course universal testing of pregnant women (with comprehensive confirmatory testing) is the only sure way of obtaining true seropositive figures. We believe, like others, that if truly anonymous, this is ethical and needs to be done at regular intervals. It would also allow us to assess the role of our present policy. This is particularly important if the refusal rate remains relatively high as we may be missing a number of seropositives as happened in a recent study of a high-risk population (Krasinski *et al.* 1988).

Addendum

Between April and July 1988 we have seen an additional three HIV-antibody-positive pregnant women. Two presented for booking at the antenatal clinic; they were not in known high-risk groups, both were born in the UK, one was a 23-year-old West Indian and the other a 23-year-old white woman. The third woman presented at the gynaecology clinic requesting termination of pregnancy.

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Congenital human immunodeficiency virus (HIV) infection in the Bahamas

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Summary. In the 13-month period between June 1985 and July 1986, 27 children were found to be HIV positive in the Princess Margaret Hospital in Nassau. Nineteen of the children had clinical AIDS, four were in the prodromal phase and four were symptom free. The clinical course of these infants is presented. Of the 18 mothers 16 were screened and were all seropositive and asymptomatic. They remained healthy in spite of subsequent pregnancies in nine of them (56%) during a follow-up period of between 13 and 65 months (mean 40 months). Fifteen of the 18 mothers were Haitian but only three had other risk factors, throwing doubt on the value of selective screening in Afro-Caribbean countries.

The Bahamas is an archipelago lying off the coast of Florida with a population of 250 000 and 5500 deliveries a year, most of which take place in the capital, Nassau, at the Princess Margaret Hospital. Acquired immunodeficiency syndrome (AIDS) had been recognized in the community since 1982 but was not diagnosed in children until 1985. This study records the clinical course of 27 children with congenital human immunodeficiency virus (HIV) infection during the period June 1985 to July 1986.

Subjects and methods

From June 1985 HIV screening (ELISA; Abbott) was performed on all donated blood, on family members of those found to be HIV positive, and those who were thought to be infected on clinical grounds alone. Positive cases were confirmed in Miami using the Western blot method. Laboratory confirmation of infections was made whenever possible.

Selection of children for testing was based on clinical suspicion in 19, because of seropositive siblings in four, and as the result of screening paternal blood donations in four.

Nineteen (70%) of the children were of Haitian parentage, although all had been born in the Bahamas.

Results

The 27 children were born to 18 mothers. One mother emigrated before testing was available and one died from salmonellosis. The remaining 16 were all found to be seropositive on screening but were symptom free.

The diagnosis of AIDS as defined by the Centers for Disease Control (1986) relies heavily on laboratory confirmation, some of which was not available to us. Using the Pan American Health Organization (1987) recommendations, 19 of the HIV-positive children were classified as having AIDS, four had AIDS-related complex (ARC), and four were HIV positive but asymptomatic.

Tables 1 to 3 summarize the available epi-

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Table 1. Epidemiology and clinical course of 19 children with acquired immunodeficiency syndrome (AIDS)

Patient no.	Age at testing (mths)	Reason for test	Risk factors	Symptoms	Laboratory results	Outcome	Siblings
1	50	Symptomatic from 1 year	Haitian mother +ve	GE, LN, H/Sp, L, M, FTT, C, An, Na ↓	HIV, T4/T8, H, EBV, CMV, K, EC, G+ve cocci	Died 3½ years after onset	Two-year-old girl not screened
2	36	Symptomatic from 7 months	Haitian mother +ve	M×2, Sep×4, FTT, LN, H/Sp, Pn, An, S-J, Na ↓ , S, L, C	HIV, T4/T8, H, St.pn, St epi, Dip, H.flu, Mantoux +ve	Died 3 years after onset	Infant no 11 and one not screened
3	7	Symptomatic from 6 months	Haitian mother +ve	GE, PI, C, H/Sp, LN, Sep×2, FTT, L, An, Na ↓ , T, S, J	Shig.fl, EPEC, CMV, Ps, HIV, T4/T8	Died 11 months after onset	—
4	17	Symptomatic from 5 months	Haitian mother +ve	LN, H/Sp, E, OM, GE, FTT, Sep	HIV, T4/T8, Ps, K, St au, Grp A Strep.	Alive 2½ years later	HIV −ve sibling (3½ years)
5	3	Symptomatic from 3 months	Haitian mother +ve	GE, FTT, C, .	HIV, T4/T8,	Died at 4 months	No 23
6	3	Symptomatic from 3 months	Haitian mother +ve	Pn, PI, GE, C, FTT, L, An, T, Na ↓	HIV, T4/T8, no bacteria isolated	Died at 10 months	Nos 25 and 26
8	8	Symptomatic from 4 months	Haitian mother +ve, father i m	Pn, FTT, An, GE, C	EPEC, HIV, T4/T8	Died at 8 months	Negative (2½ years)
9	18	Symptomatic from 8 months	Haitian mother +ve	L, H/Sp, An, C, Abs, An, GE, Sep, FTT OM, Pn	EBV, HIV, T4/T8	Died at 23 months	Three negative older siblings
10	12	Symptomatic from 6 months	Mother +ve prostitute, father Haitian NT	FTT, C, Pn, GE,, OM, . .	HIV, T4/T8,	Alive at 17 months	Nos 18 and 27 (half sister)
12	40	Symptomatic from 10 months	Haitian mother NT	Sep×2, FTT, LN, Abs, GE, Pn	Pneumococcus, St epi, HIV, T4/T8	Died at 41 months	Newborn and older siblings not tested
13	12	Symptomatic from 11 months	Haitian mother +ve	M, H/Sp, C, LN, Pn, L	TB contact, HIV, T4/T8	Alive at 1½ years	—
14	30	Symptomatic from 3 months	Haitian mother +ve, father bisexual, died of AIDS	Sep×3, Pn, FTT, C, An, H/Sp, LN, PI, L, OM	TB contact, Strep.Pn×3, EPEC, HIV	Alive at 34 months	Two older negative siblings
15	27	Symptomatic from 1 year	Haitian mother (NT) died	C, GE, Pn, LN, H/Sp, OM, Abs, FTT	HIV, T4/T8,	Lost to FU at 2½ years	—
16	26	Symptomatic from 13 months	Haitian mother +ve	FTT, Pn, PI, LN	No bacteria isolated, HIV	Alive at 25 months	No 24, 6 years old, negative
17	—	Symptomatic from . .	Haitian mother +ve	Not known	HIV, T4/T8, . .	Died	—
18	5 days	Family screen	Haitian father, mother prostitute	GE, C, FTT, OM	HIV, T4/T8	Died at 2 months	Nos 10 and 27 (half sister)
20	21 days	Father +ve blood donor	Mother +ve	GE, C, OM, FTT, Pn	HIV, T4/T8, Candida	Alive at 5 months	Nos 21 and 22
22	13	Father +ve blood donor	Mother +ve	None initially, Sep, GE, C, cellulitis at 18 months	HIV −ve at 13 months, HIV +ve at 18 months, St au	Alive at 20 months	Nos 20 and 21
23	1	Family screen	Haitian mother +ve	None until >3 months		Died at 1 year	No. 5

Key to abbreviations used in tables:
+ve, HIV positive; GE, Gastroenteritis, LN, lymphadenopathy, H/Sp, hepatosplenomegaly, L, elevated liver enzymes (LDH); M, meningitis, FTT, failure to thrive, C, oropharyngeal candidiasis, An, anaemia; Na ↓ , hyponatraemia, HIV, human immunodeficiency virus, T4/T8, reversal of the lymphocytic ratio, H, herpesvirus; EBV, infectious mononucleosis, CMV, cytomegalovirus, K, *Klebsiella*; EC, *E coli*; Sep, Septicaemia; Pn, Pneumonia; S-J, Stevens-Johnson syndrome; S, seizures; St pn, *Staph pneumonia*; St.epi, *Staph. epidermis*, Dip, diptheroids, H Flu, *Haemophilus influenza*; PI, pulmonary infiltrates (lymphocytic interstitial pneumonia or *Pneumocystis carinii*), T, thrombocytopenia; J, jaundice, Shig.fl, *Shigella flexneri*; EPEC, entero pathogenic *E coli*; Ps, *Pseudomonas*, E, eczema, OM, otitis media; St.au, *Staph. aureus*, Abs, abscess, i m., intramuscular injections from a traditional healer, NT, not tested; FU, follow-up, . . , incomplete data.

Table 2. Epidemiology of four children with AIDS-related complex

Patient no.	Age at testing (months)	Indication for HIV test	Risk factors	Symptoms	Laboratory results	Outcome	Siblings
7	14	Symptomatic from 1 year of age	Haitian father died of AIDS, mother HIV +ve	GE, FTT, L, E, LN, An	HIV +ve, . .	Alive, FTT	—
11	20	Family screen, symptomatic from 9 months	Haitian mother HIV +ve	L, FTT, An, GE	TB contact, Mantoux −ve, HIV +ve, cultures sterile	Thriving at 27 months, lost to FU	No. 2
19	72	Family screen, father +ve blood donor	Mother Haitian, father HIV +ve	LN	EBV −ve, HIV +ve, . .	Alive and well	. . .
27	3	Family screen	Mother HIV +ve prostitute, father Haitian	GE, LN, FTT	HIV +ve	Alive	Nos 10 and 18

demiological and clinical data for these groups of children.

The 19 children with AIDS exhibited clinical signs and symptoms of their disease within the first 18 months of life (range 2–18 months). They were hospitalized on 79 occasions and seen frequently as outpatients because of bacterial infections.

Children with ARC became symptomatic later in general than those with AIDS (range 3 months to 6 years). The course of the disease was variable; one child with ARC appeared to make a recovery, regaining weight (from <3rd centile to the 25th) and remaining symptom free during an 18-month follow-up period.

Of the 27 HIV-positive children 14 were less than 15 months of age when first tested (Tables 1 to 3). Nine of these developed AIDS (five have died), two have ARC, and three were symptom free at the end of the study period, although one of those (no. 23) is known to have developed AIDS subsequently. Case no. 22 is of particular interest, being one of a pair of identical twins whose first ELISA test was negative at 13 months of age. He was also without symptoms at this time but became ill and seroconverted at 18 months. The remaining members of his family, including his asymptomatic identical twin, were all HIV positive.

There were eight seronegative siblings in this study. All were older than their index case, some by several years. Four of them had different

Table 3. Epidemiology of four HIV-positive children

Patient no.	Age at testing (months)	Indication for HIV testing	Risk factors	Symptoms	Laboratory results	Outcome	Siblings
21	13	Father HIV +ve blood donor	HIV +ve mother	None	HIV +ve	Alive at 20 months	Nos 20 and 22
24	48	Family screen	Haitian mother HIV +ve	None	HIV +ve	Alive and well	No. 16
25	66	Family screen	Haitian mother HIV +ve	None	HIV +ve	Alive and well	Nos 6 and 26
26	1	Family screen	Haitian mother HIV +ve	None	HIV +ve	Alive and well at 3 months	Nos 6 and 25

fathers from the index case They had lived with a child with AIDS for a mean period of 11 months. There were no cases of seroconversion in this small group during the study period.

Nine of the infants in this study (case nos 6, 11, 16, 18, 20, 21, 22, 23, 26) were the younger siblings of HIV-positive children; the nine mothers were all seropositive. There were three children who emigrated before testing could be carried out (siblings of case nos 1, 2, 12). Six of the nine tested developed AIDS, another had ARC and the remaining two were seropositive but asymptomatic. Unfortunately no information on follow-up is available for the latter two infants.

Discussion

The children in this series showed patterns of presentation and symptomatology similar to those observed in North America and Europe (Arico *et al.* 1986; Shannon & Ammann 1985). Not all of the children with HIV infection failed to thrive; indeed one with ARC improved, as has been reported previously by Arico *et al.* (1986).

Risk factors such as concurrent infections (e.g. cytomegalovirus), poverty, the use of dirty needles, and prostitution (Drew 1986) may have played a part in this series. Women who take drugs are known to be susceptible (Ciraru-Vigneron *et al.* 1987), but this did not appear to be a factor. Almost all the patients in this study were Haitian, but they were also the poorest sector of the community and the least healthy. This heterosexual pattern of disease is consistent with earlier African and Haitian experience (Pape *et al.* 1985; Acheson 1986). The observation that all the women bar one remained healthy throughout is interesting; the one who died from salmonellosis may have had AIDS. This contrasts with the earlier belief that natural immunosuppression occurring during pregnancy adversely affects women carrying the AIDS virus (Scott *et al.* 1985). Some of the women had as many as three subsequent pregnancies and although their children and consorts may have died, they have remained asymptomatic. Similar findings have been reported by others (Ciraru-Vigneron *et al.* 1987). Our conclusion is that it may be necessary to screen the whole antenatal population in Afro-Caribbean countries in order to identify those who are infected so that they may be appropriately counselled and managed.

In the present climate of opinion, where those who are HIV positive experience difficulty obtaining employment, insurance and in many aspects of daily life, the initiation of any screening programme must be accompanied by the ability to maintain strict confidentiality (Leads from the MMWR 1986). Just how far such confidentiality should be kept remains a matter of debate.

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Variation in the T/QRS ratio of fetal electrocardiograms recorded during labour in normal subjects

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Summary. The T/QRS ratio of the fetal ECG was obtained during labour from 25 women with normal pregnancies. The poor signal-to-noise ratio of the unprocessed signals, chiefly due to baseline wander, led to a wide variation between individual measurements. This problem was overcome by data averaging, the ratio being expressed as a mean over 1-min epochs. The average T/QRS ratio of each labour record ranged from 4% to 23% with a mean of 10% (for all 25). The average range (between 5th and 95th centile) of the 1-min T/QRS ratios was 13% and there were no significant changes as labour progressed. The effect of contractions on the T/QRS ratio was measured from eight subjects and found to be inconsistent.

The poor prediction of fetal acidosis and birth state provided by continuous fetal heart rate (FHR) monitoring continues to stimulate interest in other methods of assessing the fetus during labour. Investigation of the waveform of the fetal electrocardiogram (ECG) is one attractive possibility since this is possible as soon as an electrode is attached to the fetus. In the early years of fetal monitoring, changes in the ECG waveform assumed less importance than the changes in the heart rate, partly because they were less easy to measure and partly because significant changes in the ECG waveform were thought to occur only as a terminal event (Hon & Lee 1963). More recent data have shown that changes in the fetal ECG waveform can be detected before this critical point is reached. Pardi *et al.* (1974) observed that both depression and elevation of the ST segment and elevation or inversion of the T wave could arise during or following late decelerations. Lilja *et al.* (1985) measured the T/QRS ratio and found significant increases in 14 of 27 fetuses with an abnormal FHR pattern. Jenkins *et al.* (1986) measured ST segment elevation and T wave height from 24 fetuses during labour and divided the fetuses into two groups according to the cord artery pH; a significant increase in ST elevation and T wave height was found in the acidotic group (pH<7·20). Murray (1986) has reported preliminary results from an on-going study in Nottingham in which significant displacements of the ST segment were found in 33 of 142 fetuses monitored during labour; the cord artery pH in this group (average 7·21, range 6·99–7·26) was significantly lower than in the other fetuses studied.

So far relatively little has been published about the T wave of the ECG in defined normal

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human fetuses. Marvell *et al.* (1980) analysed recordings of computer-processed ECG waveforms by eye from 37 normal fetuses at the start and end of labour. The ST segment appeared 'normal' in 87–89% of fetuses whereas the T wave had a varied appearance, being described as 'normal' in 55% at the start of labour and in 37% at the end. Computer measurement of ST segment displacement over the last 140 min of labour showed considerable variation both between patients and as delivery approached. The 14 non-acidotic fetuses studied by Jenkins *et al.* (1986) were used to define the normal range for ST elevation and T wave height; the range in the height of the T wave was considerable (coefficient of variation 27%). Thaler *et al.* (1987) recorded fetal ECG waveforms from 25 normal fetuses and showed a significant increase in T/QRS ratio during contractions.

Recording conditions can critically affect the appearance of the ECG (Greene 1987). In particular, the low frequency components of the T wave may be distorted if the ECG signals are filtered above 0·05 Hz in adults (American Heart Association 1967) while in the fetus a slightly higher level (0·16 Hz) has been suggested in view of its faster heart rate (Marvell *et al.* 1980). With frequency cut-offs in this range, baseline wander becomes a major source of 'noise', and some method of improving the signal-to-noise ratio is required for automated measurements of the ECG waveform. Various systems based upon computer averaging have been developed (Wickham 1982; Lindecrantz 1983; Kirk & Smith 1986).

Table 1. Maternal and fetal data at delivery

Variable	Mean	Range
Maternal age (years)	24·5	17–34
Gestation (weeks)	40	38–42
Birthweight (g)	3566	2720–4600
Duration of labour (h)	8·9	2·8–20·2
Duration of recorded fetal ECG (h)	4·1	1·1–11·8
Apgar score at 1 min	8·6	8–9
Apgar score at 5 min	9·1	8–10
Umbilical artery pH	7·29	7·16–7·37
Umbilical artery $P\mathrm{o}_2$ (kPa)	2·01	1·04–3·20
Umbilical artery $P\mathrm{co}_2$ (kPa)	6·71	4·06–8·30
Umbilical artery base deficit (mmol/l)	5·5	1·5–11·7
Fetal base deficit minus maternal base deficit (mmol/l)	−1·4	−5·6–4·1

Subjects and methods

The fetal ECG waveform was studied in 174 women who required continuous fetal heart rate monitoring during labour. In retrospect, 25 women were considered to be normal according to the following inclusion criteria: gestation >36 completed weeks; no antenatal complications; normal intrapartum cardiotocograph; no meconium; spontaneous vaginal delivery or instrumental delivery (for delay only); birthweight >10th centile for gestational age; Apgar score >6 at 1 min; umbilical artery pH >7·15. Of these 25 subjects, 14 were induced between 38 and 42 weeks gestation for a variety of reasons (post-dates, suspected growth retardation, poor obstetric history) and the other 11 had normal pregnancies but were monitored in labour for a number of minor problems (suspected, but unconfirmed, FHR abnormalities; delay requiring augmentation with oxytocin; short-lasting hypertension).

Fifteen of the normal subjects were nulliparous and 10 were parous. Fetal presentation in all subjects was cephalic. Twenty-one women were delivered spontaneously and four required a forceps delivery for delay in the second stage of labour. In all cases the fetal ECG was recorded for a period of at least 1 h and to within 30 min of delivery. Samples of maternal venous and umbilical artery blood were obtained from all subjects at delivery for blood gas and pH analysis (Corning 178 blood gas analyser). Further details are given in Table 1.

The fetal ECG was recorded using a single reusable Copeland electrode (Surgicraft). The signals were passed to a Sonicaid FHR monitor (Model FM3R) using a standard maternal leg plate electrode as a reference. The fetal ECG signals were filtered by the Sonicaid monitor between 0·3 and 50 Hz and processed to obtain the FHR. At the same time the ECG signals were taken from the auxiliary socket of the monitor and passed to a separate recording room, either by direct connection or by telemetry (Hewlett Packard 80210A telemeter used in diagnostic mode, 0·16–40 Hz). Contraction data, obtained by external transducer, were transferred in a similar manner. The ECG and contraction data were stored on separate channels of a Racal 'Store 4' FM tape recorder (recording speed 15/16 ips, frequency bandwidth 0–315 Hz).

The waveform of the fetal ECG was analysed off-line by computer. During replay the low frequency components of the fetal ECG signals were electronically enhanced to extend the range down to 0·1 Hz and thus compensate for the filtering of the data collection system. The upper frequency cut-off during replay was 40 Hz. The signals were then passed to a microcomputer (Adams 1984) via a 12-bit tracking A/D converter and QRS detector. The output of the A/D converter was sampled every millisecond. Three successive ECG waveforms (in the heart rate range 60–200 beats/min) were required for one measurement of the T/QRS ratio. Following identification of the 'first' QRS complex, measurements of T wave height and the peak-to-peak amplitude of the QRS complex were made from the second ECG waveform (Fig. 1). To measure the T wave height, the T wave was first smoothed using a 64-point moving window and its height (positive or negative) then measured in relation to an isoelectric line set between the 'pre-P wave regions' of the second and third QRS complexes. By arbitrary definition the 'pre-P wave region' lasted for 64 ms and ended 120 ms before the peak of the R wave; the isoelectric line joined the average values for each region (Fig. 1). For convenience the T/QRS ratio was expressed as a percentage. The time required to measure and display the T/QRS ratio meant that the 'fourth' ECG waveform was unavailable for processing; thus, at best, measurements of the T/QRS ratio could only be made from 25% of the available ECG waveforms.

Results

Data quality

There was considerable variation in the individual measurements of the T/QRS ratio due chiefly to baseline wander. This was quantified by examining in detail 100 consecutive T/QRS ratios from 10 representative subjects. The range of all 1000 T/QRS ratios was from −52% to +73%. To reduce this problem, the effect of averaging the individual T/QRS ratios in various groups was examined (Fig. 2). The range around the mean was decreased by a factor of 6 by averaging in groups of 15. Averaging in larger groups gave only a small improvement over this. It was decided to include for analysis only those minutes of data which included 15 or more measurements of the T/QRS ratio. The T/QRS ratio for a valid minute was expressed as the mean of the T/QRS ratio measurements obtained in that minute.

In the 25 subjects described in this paper the number of T/QRS ratio measurements made per minute ranged from 0 to 43 (median 21); 30% of these were discarded because there were fewer than 15 measurements (Fig. 3). The overall proportion of valid minutes in each labour record varied from 32% to 97% (median 71%). The variation in data quality during each of the 25

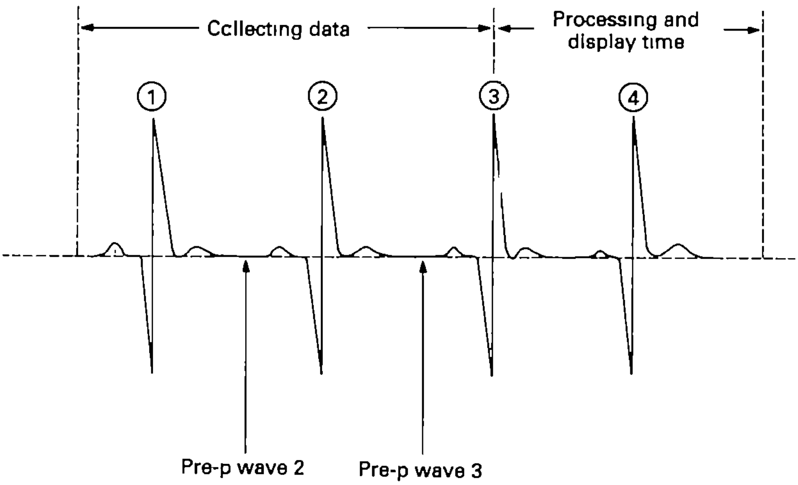

Fig. 1. Diagrammatic representation of method used to measure one T/QRS ratio. Four ECG complexes are used and the ratio obtained from the second complex (see text).

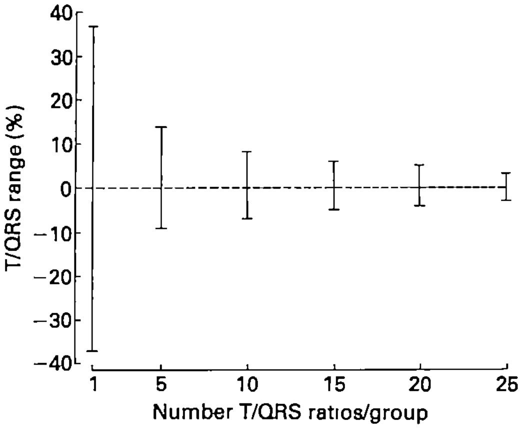

Fig. 2. The effect of group averaging on the range of T/QRS ratios around the mean One hundred consecutive T/QRS measurements were examined from 10 subjects. Each mean adjusted to zero for comparison.

recordings was also assessed: in 11 the quality was consistent throughout the recording, in seven the data were initially consistent but deteriorated during the last hour and in the remaining seven the data quality varied throughout the recording. In 17 of the 25 records some deterioration in data quality was noted during contractions, particularly with pushing in the second stage of labour.

T/QRS ratio changes during labour

The mean 1-min T/QRS ratios were studied during the recording period for each subject. A typical example of the changes in the ratio during labour is shown in Fig. 4. No significant trends were observed with time and the distribution of the values around the mean was approximately normal. The mean 1-min T/QRS ratio for all the fetuses across the whole recording period ranged between 4% and 23% with a mean value (for all 25) of 10%. The range around the mean was expressed between the 5th and 95th centile values; this expression overcame the problem of occasional outlying values. The average range for all fetuses was 13% (5th to 95th centile). Details of individual means and ranges of 1-min T/QRS ratios for each fetus are given in Table 2.

In eight of the 25 subjects preliminary observation of the effect of uterine contractions on the T/QRS ratio was possible (Table 3). To do this the T/QRS ratios measured during a contraction were averaged (provided the total was not less than 10) and compared with the T/QRS ratio averaged from the same number of ECG complexes measured during the period of uterine relaxation preceding the contraction. Using the paired *t*-test, significant changes ($P<0{\cdot}05$) were found in only two subjects: in one the T/QRS ratio increased and in the other it decreased.

Discussion

If changes in the T/QRS ratio of the fetal ECG waveform are shown to be a useful additional method of assessing fetal condition during labour, a reliable on-line method of obtaining the measurements is required. Previous descriptions of the fetal ECG waveform during labour have not presented a detailed assessment of the quality of the original ECG signals although the significance of any measurements made from the waveform will be crucially affected by this. The wide variation that we found between individual measurements of the T/QRS ratio may be ascribed to the poor signal-to-noise ratio, this being principally a consequence of low-frequency baseline wander. This problem cannot be resolved by filtering as this would also distort the T wave (Greene 1987). Lilja *et al.* (1985) reduced the baseline wander by recording the fetal ECG from two electrodes attached 2–4 cm apart on the fetal scalp, but this approach is unlikely to appeal in a clinical setting. At present all systems of automated fetal ECG waveform analysis overcome the signal-to-noise problem by using some method of averaging.

A preliminary study carried out in our own departments showed that signal averaging of the

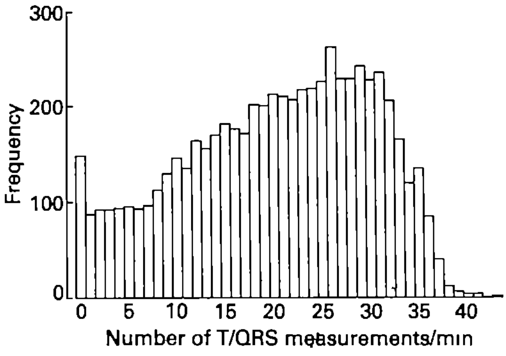

Fig. 3. Number of T/QRS measurements made per minute from 25 normal records. The system of data analysis meant that only one ECG complex in four was available for T/QRS ratio measurement.

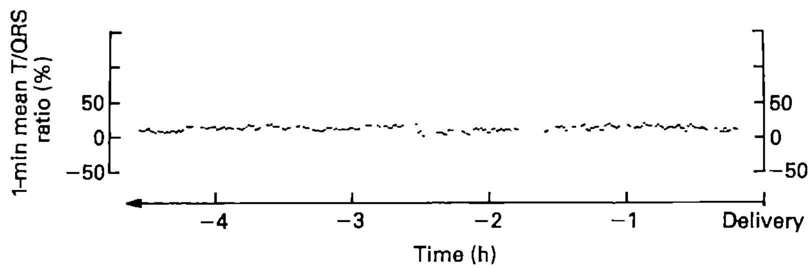

Fig. 4. Labour profile of 1-min mean T/QRS ratios from subject 2 recorded for 4·5 h before delivery. The average of the 1-min mean T/QRS values was 13%.

ECG complex could reduce the T/QRS ratio (due to variations in the QT interval) and subsequently it has been measured from individual ECG complexes. Our method of signal processing meant that measurements of the T/QRS ratio could only be obtained from one in four of the available ECG complexes (Fig. 1). This would mean that, with an assumed heart rate of 120 beats/min, 30 measurements of the T/QRS ratio would be expected per minute; in practice, however, the poor quality of the data meant that the yield of T/QRS ratio measurements per minute was frequently less than this (Fig. 3). Furthermore, for 30% of the recorded minutes, fewer than 15 individual measurements of the T/QRS ratio were obtained (Fig. 3) and thus, with our criteria, no average T/QRS ratio could be provided. Data processing with the Nottingham system appears to be more successful; in their case, measurements of the T/QRS ratio are made provided that the signal-to-noise ratio is greater than 5 after signal enhancement. Only three of 155 reported recordings had episodes where the signal-to-noise ratio fell below 6 (Murray 1986). Insufficient information is provided by other workers in this field to enable further technical comparisons between the various systems.

Our own values of the T/QRS ratio in normal labour cannot be compared with the ratio described by Jenkins *et al.* (1986) as, at that time, the Nottingham system compared the T wave height with the R wave height (and not the peak-to-peak height of the entire QRS complex). However, the average T/QRS ratio of 10% obtained from the 25 normal subjects in our study may be compared with averages for the normal of 18% and 26%, between and during contractions, obtained by Thaler *et al.* (1987), 15% obtained for normal labours by Lilja *et al.* (1988), and 20% measured during episodes of normal CTG by Lilja *et al.* (1985). It is of interest that average values for the T/QRS ratio in the healthy fetal lamb are 17–19% (Greene *et al.* 1982), but the data were collected using precordial leads which may alter the morphology of the ECG waveform.

Thaler *et al.* (1987) reported a significant increase in the T/QRS ratio during contractions in 25 normal subjects. Eight of our subjects had

Table 2. Mean and range of T/QRS ratio in 25 normal labours

Subject number	1-min T/QRS ratio (%)		
	Mean	5th centile	95th centile
1	9	−3	14
2	13	7	19
3	20	10	27
4	6	1	10
5	14	7	21
6	12	3	18
7	23	10	29
8	16	9	24
9	13	7	19
10	10	2	17
11	9	6	11
12	4	−1	7
13	15	7	22
14	4	−3	9
15	5	1	10
16	7	2	11
17	6	−6	14
18	14	1	23
19	6	−3	11
20	9	1	14
21	12	3	18
22	7	−1	15
23	5	0	10
24	5	1	9
25	16	13	25
Average	10·4	3·7	16·3

Table 3. Average T/QRS ratio measurements between and during contractions

Subject number	Record length (min)	Number of contractions suitable for measurement	T/QRS ratio (%) Between contractions Mean (SD)	T/QRS ratio (%) During contractions Mean (SD)	*P*-value*
2	274	89	13 (4)	14 (4)	NS
4	274	59	6 (3)	6 (4)	NS
8	370	87	17 (6)	1 (5)	0·0005
9	336	95	13 (3)	12 (3)	NS
12	234	41	4 (3)	3 (3)	NS
23	710	180	5 (3)	5 (4)	NS
24	247	49	5 (4)	4 (3)	NS
25	380	99	16 (5)	18 (7)	0·005

* Paired *t*-test.
NS, Not significant

contractions data of sufficient quality to enable us to investigate this; in only one was there a significant increase in the ratio during contractions. A visual analysis of our unprocessed ECG records suggests that during contractions there is more baseline wander and we feel that the influence of this problem should be considered before the changes in T/QRS ratio reported by Thaler *et al.* (1987) are assumed to reflect a decrease in the oxygen supply to the normal fetus as they have postulated.

The signal processing needed to obtain the T/QRS ratio is substantially more complicated than that required to obtain the fetal heart rate. At present the Nottingham system (UK) is under a commercial patency application while another system developed by K. G. Rosen and his colleagues in Gothenburg, Sweden, is on trial in a number of hospitals. In due course it will be important to compare the performance of the various systems directly. Preliminary bench tests between the system described in this paper and the one used in Nottingham indicate that, provided the quality of the data was good, the measured trends in the T/QRS ratio were similar.

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Umbilical artery flow velocity waveforms in labour

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Summary. Doppler signals were recorded from the umbilical arteries in 103 women during labour. The pulsatility index (PI) did not alter with progress in labour. During uterine contractions the PI showed a change only if there was a deceleration in the fetal heart rate. Low birthweight (< 10th centile) and delivery by caesarean section for fetal distress were significantly more frequent in patients with abnormal PI values (defined as >2 SD above the mean in normal labours). Fetal scalp blood pH was measured in 24 patients. The PI was abnormal in only one case, but none of the 24 had a pH <7·20.

Doppler ultrasound has been widely reported as a non-invasive technique for studying changes in blood flow velocity in the umbilical arteries. Most investigators have examined the relation between the flow velocity waveform (FVW) and antepartum complications, in particular fetal growth retardation (Fleisher *et al.* 1985; Erskine & Ritchie 1985) and pregnancy-induced hypertension (Trudinger *et al.* 1985). However, Doppler ultrasound is also a suitable method of investigating the umbilical circulation in labour

The umbilical artery FVW is influenced by many factors including downflow resistance, cardiac output and heart rate. In fetal lambs, hypoxia is associated with a redistribution of blood flow towards the vital organs (Block *et al.* 1984; Jensen *et al.* 1985). It is possible that the human fetus subjected to intrapartum hypoxia responds in a similar way and this response may be associated with a change in one or more of the factors which determine the umbilical artery FVW pattern.

This paper describes an investigation of the FVW at different stages of normal and abnormal labour, the effect of uterine contractions and the association between the umbilical artery pulsatility index (PI) and outcome of labour.

Subjects and methods

A total of 103 women was recruited from the labour ward in Glasgow Royal Maternity Hospital. Labour was induced or augmented with oxytocin or prostaglandin in 74 and progressed spontaneously in 29. Doppler signals were recorded from the umbilical artery using a Vasoscan continuous-wave Doppler system with a 4-MHz transducer and a 200-Hz thump filter to exclude low-frequency distorting signals. The umbilical artery was easily identified by its characteristic biphasic FVW and the presence of the non-pulsatile umbilical vein alongside. At each examination the patient was in a semi-recumbent position with her head and chest supported at approximately 45° to the horizontal. Recordings were taken between and during contractions, before and after amniotomy, early in the first stage (cervix <5 cm dilated), late in the first stage (cervix ≥5 cm dilated) and in the second stage of labour. Nitrous oxide/oxygen mixture, intramuscular pethidine and epidural analgesia were available for pain relief and the

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type of analgesia was determined primarily by the woman herself.

Small-for-gestational-age (SGA) was defined as a birthweight < 10th centile according to the birthweight-for-gestational-age standards in a Glasgow population (Forbes & Smalls 1983). In all women the fetal heart rate (FHR) was monitored continuously with an abdominal ultrasound transducer or a fetal scalp electrode. Labour with late or variable FHR decelerations with or without loss of short-term variability was defined as abnormal. Labour without these FHR patterns was defined as normal. Labour with early decelerations or occasional variable decelerations was included in the normal group. The diagnosis of fetal distress prompting operative intervention was made by the obstetrician responsible for the management of labour and was usually associated with persistent FHR abnormalities with or without a fetal scalp blood pH of <7·25. Neonatal condition at birth was assessed by the 5-min Apgar score.

Waveforms were analysed with a Doptek spectrum analyser. Five waveforms were examined from each recording and a mean value for the PI was derived. The Doppler results were not revealed during the study. A normal range of umbilical PI at each stage in labour was defined, after completion of the study, as the mean PI ±2 SD calculated from all normal labours resulting in an infant with a birthweight >10th centile. Any PI value >2 SD from the mean was thus classified as abnormal.

A preliminary variability study was performed to investigate the reproducibility of intrapartum Doppler recordings. In 20 women, umbilical artery FVWs were recorded on at least three occasions during labour by two independent observers. The mean intra-observer variation (mean coefficient of variation for 20 patients) was 8·3% for each observer. Inter-observer variation was investigated by calculating the difference between the mean PI recorded by the two observers for each patient studied. The average inter-observer difference in PI recordings for the whole study group was 0·033 which was equivalent to an average change in the PI value of 3·5%

Statistical analysis

The distribution of umbilical artery PI for recordings between contractions at each stage in normal and abnormal labour was studied by constructing 10 histograms. SGA pregnancies were excluded. In most cases, the distribution was not normal. Non-parametric tests, Mann–Whitney *U*-test, Wilcoxon matched pairs two-tailed test and Fisher's test were selected for comparing the data.

Results

The pregnancy and delivery details subdivided into normal and abnormal labour groups (Table 1) showed that the mean birthweight and gestation were similar in both groups ($P>0{\cdot}05$, Mann–Whitney *U*-test). Although there were more infants below the 10th birthweight centile in the abnormal group ($P<0{\cdot}02$), there was no statistically significant difference in the proportion of infants below the 5th birthweight centile. The frequency of antepartum complications, operative delivery for fetal distress and epidural analgesia was significantly higher in the abnormal labour group ($P<0{\cdot}001$).

PI in normal and abnormal labour (Table 2)

Women who gave birth to a SGA fetus were excluded from this analysis. All the recordings were taken between contractions when the FHR was normal. There was no change in the umbilical artery PI in either group as labour progressed This was demonstrated by comparing mean values at each stage of labour and also by comparing paired values from the same patient at different stages of labour It was not possible to obtain a full set of recordings in every patient since some women who were delivered by caesarean section did not reach the second stage, others presented in established labour with ruptured membranes and, in some instances, maternal pushing efforts made second-stage recordings impossible. No patient was excluded because of failure to obtain serial Doppler recordings and as a result there were 13 labours in which only one reading was obtained.

PI in labours associated with SGA infants

There were insufficient numbers in this group to analyse normal and abnormal labours separately. A wide range of waveform patterns was observed. Serial recordings were obtained in 14 women and a single recording in six (Fig. 1). Although serial recordings showed no change in the umbilical artery PI as labour progressed, a

Table 1. Pregnancy and delivery details in normal and abnormal labour groups

	Normal labour (*n*=60)	Abnormal labour (*n*=43)
Mean gestation (weeks)	40·0	39·4
(range)	(37·0–42·0)	(34·5–41·5)
Mean birthweight (kg)	3·37	2·99
(range)	(2·42–4·27)	(1·60–3·90)
Birthweight <10th centile	7	13*
Birthweight <5th centile	5	9
Antepartum complications (other than SGA)	2	13**
Mode of delivery		
Spontaneous vaginal	44	10**
Operative delivery for delay		
Total	13	13
Forceps	8	9
Caesarean sections	5	4
Operative delivery for fetal distress		
Total	3	20**
Forceps	3	8
Caesarean sections	0	12
Epidural analgesia	22	32**
5-min Apgar score <7	0	1

* *P*<0·02, ** *P*<0·001 (Fisher's test).

complete set of recordings was achieved in only two patients, reflecting the high frequency of operative intervention in this group.

Factors associated with an abnormal PI

Patients with a normal umbilical artery PI were compared with patients with an abnormal PI (Table 3). In seven women, both normal and abnormal PI values were recorded during labour. These women were allocated to the abnormal PI group. There was a higher frequency of epidural analgesia, SGA infants and caesarean sections or forceps deliveries for fetal distress, and a lower frequency of spontaneous vaginal deliveries in women with abnormal PI values in labour. The Apgar score at 5 min was similar in both groups.

Effect of uterine activity on the FVW pattern

In the absence of FHR abnormalities, uterine contractions had no effect on the umbilical artery PI. However, in abnormal labour, where contractions were associated with decelerations of the FHR, there was usually loss of end-diastolic frequencies during the deceleration (Fig. 2a). As the FHR returned to a normal baseline rate at the end of the contraction, the FVW also returned to its pre-contraction pat-

Table 2. Umbilical artery pulsatility index (PI) at each stage of labour in normal and abnormal labours

	Normal labour (*n*=53)		Abnormal labour (*n*=30)	
Stage of labour	PI	No. of readings	PI	No. of readings
Pre-amniotomy	0·85 (0·11)	32	0·91 (0·16)	15
Post-amniotomy	0·83 (0·12)	32	0·89 (0·17)	15
Early first stage	0·87 (0·12)	41	0·92 (0·15)	26
Late first stage	0·89 (0·11)	33	0·93 (0·16)	23
Second stage	0·88 (0·16)	22	0·95 (0·17)	16

Results are mean (2 SD) values.

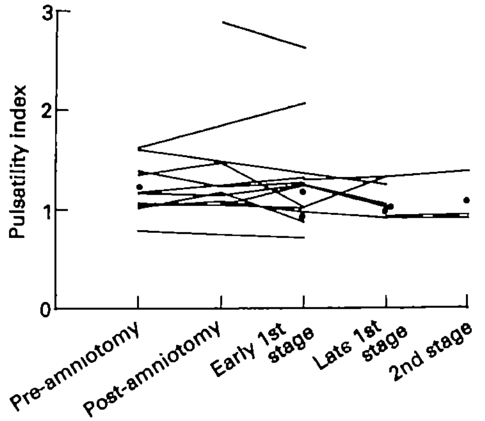

Fig. 1. Recordings of umbilical artery pulsatility index in 20 patients who gave birth to small-for-gestational-age infants. ●, Single readings; ___, serial recordings.

tern. Occasionally the FHR would decelerate during a contraction without showing any change in the end-diastolic frequencies (Fig. 2b).

Effect of uterine activity on PI in abnormal labours

The PI between contractions was compared with the PI at the depth of a FHR deceleration during a subsequent contraction. Patients where FHR abnormalities prompted operative delivery were analysed separately (Fig. 3a) from those where FHR abnormalities did not prompt operative intervention (Fig. 3b). There was a significant increase in PI during all contractions associated with FHR decelerations (*P*<0·005). Although the change in PI during a contraction appeared to be greater in abnormal labours that resulted in operative delivery for fetal distress (Fig. 3a) compared with abnormal labours where operative delivery for fetal distress did not occur (Fig. 3b), the percentage change within the two groups was not significantly different (*P*>0·05 Mann–Whitney *U*-test). The percentage change in FHR during a contraction was also not significantly different between these two groups.

Correlation between PI and fetal blood pH

The umbilical artery PI was recorded between contractions during fetal blood sampling in 24 patients (Fig. 4). The indication for sampling was persistent FHR decelerations in 20 and fetal tachycardia in four. Of the 24 fetuses, 21 had a pH >7·25. Three had a pH <7·25 but >7·20. There was only one fetus with an abnormal umbilical artery PI. This was a SGA infant with a birthweight <5th centile. Scalp pH was 7·33. Two of the three fetuses with scalp blood pH <7·25 were below the 5th centile birthweight. None of the 24 fetuses had a 5-min Apgar score <7.

Discussion

Umbilical artery Doppler studies are feasible during labour and the procedure was well tolerated by our patients. Good quality Doppler signals were obtained between contractions at all stages of labour. During contractions the Doppler signal may be lost for short periods particularly during maternal pushing efforts. It was not possible to obtain a full set of five serial recordings for each of the 103 labours studied. This reflected the difficulty of making serial measure-

Table 3. Pregnancy and delivery details in labours with normal and abnormal pulsatility index (PI) values

	Normal umbilical PI (*n*=83)		Abnormal umbilical PI (*n*=20)	
Characteristics	*n*	(%)	*n*	(%)
SGA infants	8	(10)	12	(60)**
Antepartum complications other than SGA	8	(10)	3	(15)
Spontaneous vaginal delivery	50	(60)	4	(20)**
Forceps delivery for fetal distress	6	(7)	5	(25)*
Caesarean section for fetal distress	5	(6)	7	(35)**
Epidural analgesia	39	(47)	15	(75)*
5-min Apgar score <7	1		0	

* *P*<0·05>0·01 Fisher's test.

** *P*<0·005 Fisher's test.

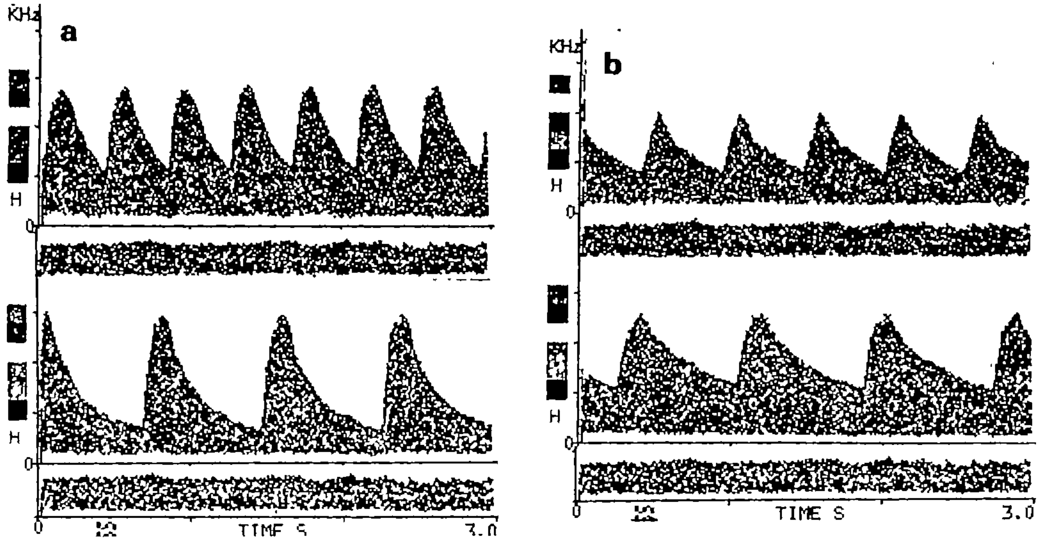

Fig. 2. Abnormal labour: umbilical artery flow velocity waveform showing (a) loss of end-diastolic frequencies, and (b) no change in end-diastolic frequencies, during a deceleration in the fetal heart rate

ments in labour rather than problems with the technique of recording the intrapartum umbilical artery FVW In this study, sufficient serial data were obtained to indicate that the umbilical artery PI does not alter during labour. If this technique were found to be useful in clinical practice, serial recordings would be necessary only to establish a normal range. Thereafter a single recording could be regarded as representative of the labour.

Intra-observer variation and inter-observer variation were no greater than values reported in antepartum reproducibility studies (Murrills *et al.* 1987). More physiological variation in intrapartum compared with antepartum Doppler recordings might be anticipated. This was not our experience and may be related to the Doppler signal being less affected by fetal movements and breathing in labour.

The indices most commonly used to describe the FVW in obstetric Doppler studies are the pulsatility index (Gosling & King 1975), the

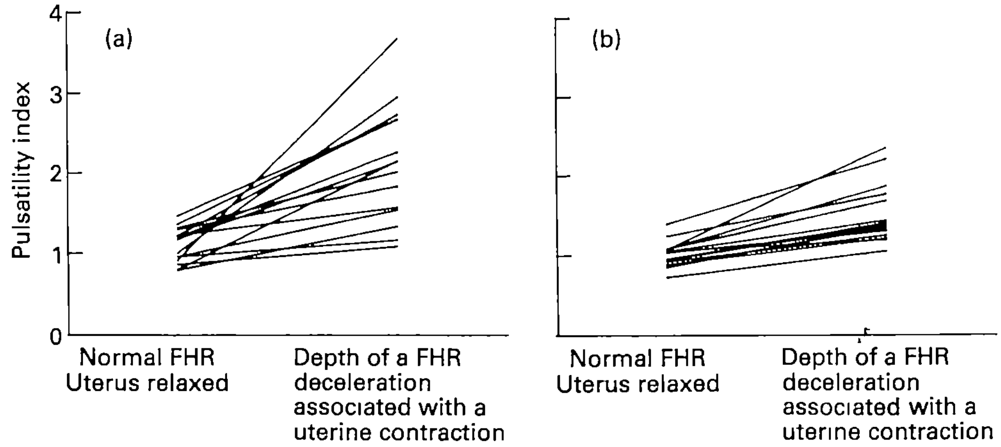

Fig. 3. Abnormal labour (a) with and (b) without operative intervention for fetal heart rate (FHR) abnormalities. A comparison between umbilical artery pulsatility index (PI) between contractions with a normal FHR and PI during a contraction at the depth of a FHR deceleration.

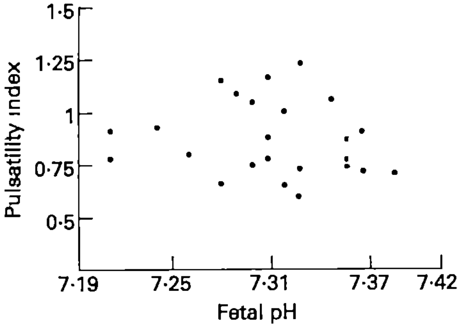

Fig. 4. Umbilical artery pulsatility index and fetal scalp blood pH.

resistance index (Pourcelot 1974) and the A/B ratio (Stuart *et al.* 1980). We calculated all three indices for each waveform analysed in our study and although we chose the pulsatility index for presenting our data, we observed the same trends and significant changes using the other two indices.

Stuart *et al.* (1981) performed Doppler studies in spontaneous labour without FHR abnormalities or epidural analgesia. Our group of normal labours included spontaneous and induced labour and 37% of patients received epidural analgesia. Despite these differences we agree with Stuart *et al.* (1981) that in normal labour the umbilical artery FVW is unaltered by amniotomy or uterine contractions. In addition, we studied the influence of progress in labour but found no change in the pattern between contractions from before amniotomy to second stage.

The abnormal waveform patterns associated with decelerations in the FHR could be due to a prolongation of diastole resulting in apparent loss of end-diastolic frequencies. Although the FHR may be a major determinant of the FVW in labour, we suggest that it is not the only factor involved. We noted that occasionally the FHR fell markedly but there was virtually no change in the PI.

One of our aims was to establish whether the umbilical artery FVW altered in acute asphyxia. Although there appeared to be a greater change in the PI during contractions in abnormal labours that resulted in operative delivery for fetal distress compared with abnormal labours without operative delivery for fetal distress, the difference between the two groups was not statistically significant. The trend could not be explained by a greater change in FHR during a contraction in the fetal distress group. There was no evidence that any of the infants in our series were asphyxiated, and a clinical diagnosis of fetal distress based on FHR abnormalities cannot be equated with fetal asphyxia. However, the change in the umbilical artery FVW during a contraction associated with a FHR deceleration is interesting and deserves further investigation.

Fetal acidosis is a component of asphyxia. We examined the relation between PI and fetal scalp blood pH in 24 fetuses and found that a normal PI was consistently associated with a fetal pH>7·20. There were no truly acidotic fetuses (pH<7·20) in this series to allow us to test the hypothesis that acidosis reflects hypoxia which leads to redistribution of blood with a change in the umbilical artery FVW. However, if a normal umbilical artery FVW is consistently found to be associated with a fetal scalp pH>7·20, Doppler studies could perhaps provide a non-invasive alternative to fetal blood sampling to confirm fetal well-being. One fetus studied had a normal scalp pH but an abnormal umbilical artery PI. The fetus was below the 5th centile and an association between abnormal umbilical artery flow velocity waveforms and low-birthweight centile is now widely recognized (Laurin *et al.* 1987).

Birthweight <10th centile or operative delivery for fetal distress or both occurred significantly more often in labours associated with abnormal PI values. Birthweight < 10th centile defines a population with an increased risk of fetal asphyxia. Hence measurement of the umbilical artery PI may prove to be a useful screening test in early labour to detect the low-birthweight fetus at risk of developing FHR abnormalities. Equally important, it might prove to be of value in selecting those who do not require continuous FHR monitoring.

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Maternal weight, weight gain and birthweight at term in the rural Tanzanian village of Ilula

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Summary. In an area-based study in a rural Tanzanian village, the relations of maternal weight and weight gain during pregnancy to birthweight were analysed for 331 term deliveries. The distribution of body-mass index, used as an indicator of maternal nutritional status, was similar to the pattern seen in Sweden, although mean maternal height (156 cm) was 9 cm below that of Swedish women. Mean initial weight measured at week 14 was 53 kg and total pregnancy weight gain was 6 kg. Women weighing ≥60 kg in early pregnancy gained less weight (0·16 kg/week) than those weighing <50 kg (0·22 kg/week). Birthweight was correlated both with maternal weight in early pregnancy and with weight gain during pregnancy, but only 10% of the variation in birthweight was explained by these maternal factors. Mean maternal weight 24 h postpartum was equal to the weight at 14 weeks of pregnancy, implying, on the average, no net weight gain. Women with a positive net weight gain had heavier babies than women with a negative net weight gain. Maternal anthropometric characteristics are important underlying determinants of intrauterine growth and birthweight, but they explain only a minor part of the variation and are of little value for screening purposes in individual women.

A positive correlation between maternal anthropometric variables and infant birthweight has been demonstrated in many studies of populations with different social and economic characteristics, mostly in developed countries (Rush 1982; Abrams & Laros 1986). Monitoring of maternal weight during pregnancy in antenatal care has therefore been advocated as an indicator of the risk of a low-birthweight baby and an adverse perinatal outcome. Wray (UNICEF 1985) has also recommended such monitoring as a basis for nutritional intervention during pregnancy.

Systematic studies of these relations in developing countries are not numerous (Gwatkin *et al.* 1981; Barron & Thomson 1983; Bantje 1986). However, they are of special interest in populations where nutritional deficiencies are common and are often combined with a heavy female workload, even during pregnancy, and where a low birthweight ranks as the most important determinant of perinatal mortality and morbidity (Petros-Barvazian & Behar 1978).

Recently a multicentre in-depth study investigated maternal body-weight measurements, among other factors, as indicators of energy balance during pregnancy both in developing

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and developed countries (Lawrence *et al.* 1987; Durnin 1987). The results show considerable variation in maternal anthropometry, especially weight gain, between the countries studied. However, the mean weight gain, expressed as a percentage of the initial weight, for all studied populations except for Gambian village women, was 17 to 20%. Gambian unsupplemented women, on average, gained only 7·3 kg (12% of their initial weight), but still had babies with a mean birthweight equivalent to that in Thailand and the Philippines, where pregnant women had a weight gain of 8·9 and 8·5 kg, respectively.

No reports appear to have been published on area-based studies of maternal weight as recorded in routine antenatal care in unselected pregnancies in developing countries. As part of a more comprehensive investigation of antenatal care in a rural Tanzanian setting, in the village of Ilula, we have studied maternal weight indices and their possible use as risk indicators during pregnancy. This report is focused mainly on the relation between maternal weight measurements and infant birthweight at term.

Background information

Study area

The Ilula study is a prospective area-based investigation of pregnancy course and outcome. Further investigations on maternal and infant nutrition were made in co-operation with the Tanzania Food and Nutrition Centre (TFNC). A brief description of the study population will be given here.

The village of Ilula is situated 1300 m above sea level along the main Dar es Salaam–Lusaka road. It is located in the Iringa region, 47 km east of Iringa town. The area is hilly with conspicuous scattered rocks but adequate for agricultural purposes. There are two periods of rain and the mean annual rainfall is 1100 mm, with large annual variations. Day temperatures are usually 20–25 °C, at night falling some 10 °C, 7 °C being the lowest and 30 °C the highest recorded temperatures. Nearly all the houses are constructed of mud. Neither electricity nor telephone is available in the area.

The staple foods are maize, beans and sunflower seeds. On the hillslopes tomatoes are grown for the Dar es Salaam market. At least 40% of the households have some kind of livestock. Preliminary findings from a survey in the same population indicate an energy deficit in relation to current recommendations of about 30%. Protein requirements are met mainly from vegetable sources.

The population

The area is inhabited by the Hehe and Bena people. Main religions are Christian (87%) and Muslim (12%). Farming is the occupation of 80% of the men and of all women. The women perform the domestic and agricultural tasks that are usual for women in rural Tanzania, with seasonal hoeing, harvesting, and tending tomato plants, seasonally involving hard physical work. Water is carried from the communal tap, which is within 1 km from most houses. Sticks and stems are used as fuel, and are often carried from considerable distances.

The mean age at first birth in this population was 18 years. In general the younger women were literate and had had 7 years of primary school, but 40% of all women had had no formal schooling and were illiterate. At a survey in April 1985, it was found that children under 5 years constituted 30% of the population, compared with 19% in the whole Iringa region. Malaria was perceived as the main health problem by the villagers. Visible goitre was present in 10% of the women in this survey of all women, pregnant and non-pregnant, a sign of the endemic iodine deficiency. An 'anaemia' prevalence of 23%, as determined by clinical inspection of mucous membranes, was found. Contraception was practised very sparsely with only 14 of 222 interrogated women using oral contraceptives and one an intrauterine device. Average core family size was five in the survey population of 541 households.

Choice of study area

Two villages in the Ilula ward, Ilula-Isere and Ilula-Mtua, henceforth referred to as Ilula, were chosen for the present study for many reasons. They are quite easily reached by road, but are still so far away from the nearest hospital—the Iringa Regional Hospital—that 91% of the women are delivered in the village. Of 707 deliveries studied, 9% took place in the hospital, and of these, 90% were referred cases.

Overall, 23% of the deliveries occurred at home, and 68% took place in a local dispensary. This dispensary has a delivery room and also provides beds for mothers to stay 1 or several days after delivery. Separately there are 20 beds available for general medical patients. A maternal and child health (MCH) clinic is run 5 days/week. The dispensary is headed by a rural medical aide.

Through attendance-promoting measures in co-operation with the political leaders, over 99% of the pregnant women with pregnancies reaching the third trimester, among the study population, paid at least one visit for antenatal care (ANC). The mean number of visits was 6·3 per pregnancy.

Patients and methods

Beginning in June 1983, all pregnancies and deliveries within Ilula were included successively in the study. Up to November 1985, when the recruitment of patients was stopped, there had been a total of 707 deliveries, 682 single and 25 twin.

The data were collected by the regular village midwife, who was employed temporarily for this study as a full-time field worker, doing antenatal work and conducting interviews after delivery. She had only intermittent contact with the study co-ordinators. Although she had a very good rapport with the study population, and the maternal and child outcome was known for over 99% of the subjects, the data were incomplete in that some questionnaires or antenatal cards were missing or some information in them was lacking. For this reason we used subgroups for different purposes. As far as we were able to check, the subgroups did not differ from the total study population in respects other than that their records were more complete and that some of them had registered early in pregnancy for antenatal care. In Table 1 some characteristics of the total study population ($n = 707$) are given together with those of the main study group ($n = 331$) and the early attenders (EA) group ($n = 68$) defined below.

For inclusion in the main study group analysed in this paper, 331 women with singleton pregnancies (Table 1) fulfilling the following criteria were selected: weight should have been recorded at registration for antenatal care and again within 10 days before delivery; the observation period from registration to delivery should have been at least 8 weeks; the length of gestation at delivery should have been over 37 completed weeks; and the birthweight of the infant should have been recorded within 48 h of delivery The mean observation period for this subset was 18 (range 9–30) weeks.

The health status of the women was average for populations in rural Africa. When interviewed after delivery, 24% of women stated that they had had at least one malarial attack during pregnancy. No epidemics or severe diseases

Table 1. Some characteristics of the Ilula study population and two subgroups, the main study group ($n = 331$) and the group of early attenders (EA) ($n = 68$)

	EA group	Main study group	Total Ilula study population
Number	68	331	707
Age (years)	26	26	25
Parity	3·0	2·8	3·0
Number of children alive	2·4	2·4	2·4
Height (m)	156	156	156
Years of education			
Primipara	6	6	6
Multipara	3	3	3
Primipara (%)	13	17	17
Home births (%)	16	16	23
Mean observation period (weeks)	26 (3·0)	18 (5·0)	15 (7·5)
Gestational age at delivery (weeks)	40·0 (1·5)	40·4 (1·9)	39·6 (2·7)
Perinatal mortality rate/1000 births			82
Twin pregnancies (n)	—	—	25
Mean birthweight of singletons (g)	3145 (395)	3160 (415)	3070 (485)

Results are means (SD) where appropriate.

occurred in the study period and only occasional admissions to hospital for other than obstetric complications, malaria or transfusion were reported.

For calculation of early pregnancy weights, 68 of these 331 women, registering before 18 completed weeks gestation (mean 14 weeks), were identified. These will be referred to here as early attenders (EA). They were followed for an average of 26 weeks (range 22–30). The characteristics of these women did not differ from those of the other groups described in Table 1. Their initial weights were considered to be representative of the maternal weight at 14 weeks in the whole study population. For 56 of them, postpartum weight was recorded within 48 h (mean 20 h) of delivery, and the net weight gain was calculated by subtracting their first recorded weights from their postpartum weights.

Examination methods

The subjects were followed up at the antenatal clinic run by the dispensary staff. The determination of the length of gestation was based on the woman's recollection of the date of her last menstrual period; 60% said they were sure of the last date, while 40% stated their last menstrual period within 10–14 days. As defined above, the study was based on term deliveries, and accordingly the mean length of gestation at delivery in the 331 women of the main study group was 40·4 weeks. We were not able to confirm the length of gestation with any specific tests. However, the distribution of gestational age at delivery among the 707 women in the total population gives some credibility to the accuracy of the determinations.

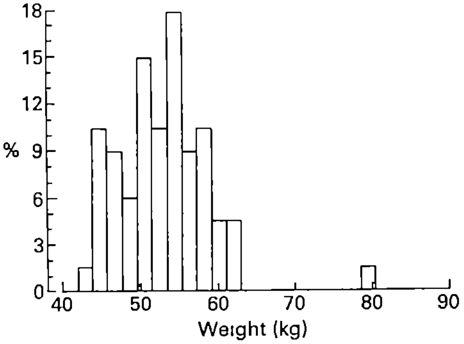

Fig. 1. First recorded weight of early attenders ($n = 68$) for antenatal care. Mean weight 53·1 kg

The official Tanzanian antenatal card (Essex & Everett 1977), with tick boxes for defined antenatal risks and recommended interventions, was used to monitor measurements and events during pregnancy. Weight was measured to the nearest kilogram on the scale (Råd och rön 1987) used at the ANC clinic.

Weight increase/week was calculated by subtracting, for each subject, the first recorded weight from the last, which was nearly always obtained within a week before delivery, and dividing the difference by the number of weeks of observation. Net weight gain was obtained by subtracting the first recorded weight from the weight within 48 h after delivery.

Body-mass index (BMI) was calculated according to the formula weight/(height)^2 (kg/m^2). For the EA group the calculated BMI based on the first recorded weight is believed to be close to the prepregnancy BMI, as the weight increase during the first 14 weeks of pregnancy in women of rural areas in developing countries is usually about 1 kg or even less (Lawrence *et al.* 1987; Hytten & Leitch 1971).

Statistical analysis

All data management has been done on a personal computer. For statistical analyses and graphs the Statgraphics package has been used. To test differences between groups, Student's *t*-test for unpaired values was used. Linear regression is estimated according to least squares method using one independent variable. A multiple linear regression analysis was done to determine the relative contributions of maternal height, weight and weight gain during pregnancy to the infant birthweight.

Results

The distribution of the 68 early attenders with respect to their first recorded weights (mean 52·7; SD 6·3 kg) is given in Fig. 1. The mean first recorded weight for all 331 women was 54·7 (SD 7·0) kg, at a mean gestational age of 23 (SD 5·4) weeks.

Mean maternal weight for length of gestation of the 68 early attenders is given in Fig. 2 as a simple linear regression line. The regression line for those subjects who registered at 18 weeks or after conforms nearly exactly. Calculations

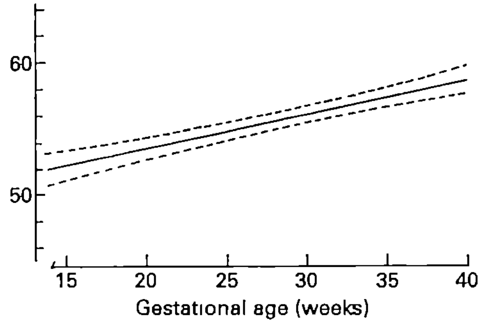

Fig. 2. Weight for gestational age based on 338 measurements in the 68 early attenders. The linear regression line is solid, SEM broken.

made for 670 of the 707 pregnancies where this was possible, and also separately for those who stated that they were certain of the date of their last menstrual period, all indicated a linear weight increase with gestation up to 40 weeks, and all weight curves conformed within 0·5 kg at each stage of gestation up to 40 weeks. Mean weight at 28 weeks was 55·7 kg (SD 7·7) for the EA group, 55·3 kg (SD 7·0) for the others. We were not able to demonstrate any association between weight and parity.

The distribution of weight increase/week is given in Fig. 3. The average weekly weight increase was 0·2 (SD 0·15) kg. For the 26 weeks from weeks 14 to 40, this increase implied a total weight gain of 5·2 kg. The mean weight gain relative to the initial weight was about 10%. There was a wide individual variation in weight increase among the women, and about 12% did not gain weight or even lost weight during the observation period.

The weight gain in pregnancy varied according to the early pregnancy weight. The average maternal weight increase/week in women with a first recorded weight of <50 kg was 0·22 kg compared with 0·16 kg/week in those starting at ≥60 kg.

The mean postpartum weight, based on measurements in 56 early attenders within 48 h after delivery, was 52·6 (SD 6·4) kg, while their mean first recorded weight was 52·4 kg. There was no significant difference in weight lost from the last weight before delivery between women weighed within the first day postpartum (4·8, SD 1·2 kg; $n = 46$) and those weighed on the second day (4·9, SD 1·2 kg; $n = 10$).

Figure 4 shows the relation between mean early weight, predelivery weight and postpartum weight in those 56 subjects in the EA group for whom the post-delivery weight was recorded. The net weight gain was on average nil, i.e. the mean weight at 14 weeks gestation was regained within 20 h of delivery. The women with a positive net weight gain had on average gained 7·6 kg during pregnancy but were at the start of pregnancy 3 kg lighter than women with a negative net weight gain (Table 2).

The maternal height averaged 156 (SD 4·4) cm. Body-mass index (Fig. 5) was calculated on the basis of early weight in the 68 women in the EA group; they had a mean BMI of 21·5 which may be regarded as an approximation of the prepregnancy BMI. In the main group of 331 women, the mean BMI at 23 weeks was 22·5, 1 unit above that of the early attenders at 14 weeks. In the EA group 28% had an initial BMI of ≤20. These women gained 0·22 kg/week, compared with a 0·18 kg weight gain/week in women with a BMI of >20.

To determine the relative importance of maternal anthropometric variables for birthweight, a multiple regression analysis using maternal height, first recorded weight and weight increase/week was performed (Table 3). First weight and weight gain during pregnancy were highly significant determinants of birthweight, while maternal height never reached statistical significance. For each extra maternal kg at registration, the birthweight was 15 g higher. Similarly, each extra kg of weight gain during the observation period corresponded to a 26 g increase in birthweight. For example, a woman who started at 50 kg at 23 weeks and gained 4 kg during pregnancy would be statis-

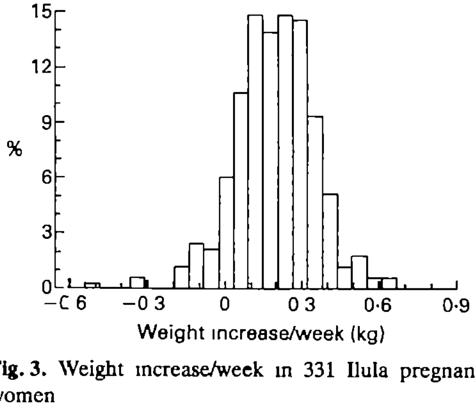

Fig. 3. Weight increase/week in 331 Ilula pregnant women

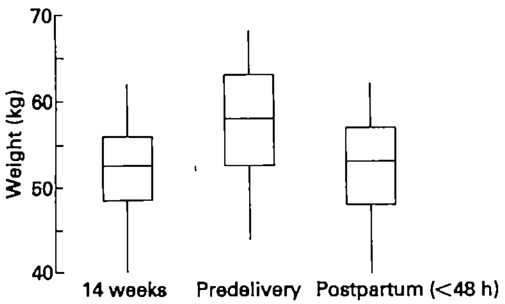

Fig. 4. Weights at 14 weeks, before delivery, and postpartum in 56 term Ilula women. Boxes indicate interquartile range, vertical lines indicate ranges and mid-horizontal bars indicate median.

tically likely to have a baby with a birthweight of 3081 g (Table 3) (2230 g + 4 × 26 g + 50 × 15 g = 3081g). However, there was a wide variation in birthweight, and maternal weight and weight gain could only explain 10% of the variation in birthweight.

One prerequisite for this model is that the effect on birthweight of pregnancy weight gain is similar for women starting at low initial weights and those starting at higher weights. This was tested by introducing an interaction term multiplying initial weight and weight gain. This factor was not significant ($P = 0{\cdot}92$) when entered into the model, thus supporting the model.

In Fig. 6 this relation between maternal weight, pregnancy weight gain and birthweight is further illustrated. In each weight group a better pregnancy weight gain resulted in a higher mean infant birthweight. Apart from a slight, insignificant aberration in the group with best weight gain, in all groups a higher first weight also resulted in a higher mean birthweight. For the women in the heaviest category with the best weight gain, mean birthweight was 3370 g.

The 27 women in the EA group who had a positive net weight gain (Table 2) had babies with a mean birthweight of 3300 g, which was significantly higher ($P = 0{\cdot}02$) than the mean birthweight of 3060 g in the 29 women who had a negative net weight gain. Infants weighed within 24 h of birth were 30 g heavier than those weighed on the second day. This difference was not significant.

Discussion

Weight is one of the maternal characteristics that is most often recorded during pregnancy, even when resources for antenatal care are very restricted. The reasons for this have varied through the years (Hytten & Leitch 1971). In developing countries the possible relation between limited availability of food on the one hand, and the high prevalence of low-birthweight babies and the high perinatal mortality rate, on the other, has aroused the interest of national and international agencies (UNICEF

Table 2. Maternal anthropometric variables and infant birthweights for 56 early attenders grouped according to the net weight gain

	Net weight gain		Significance level
	Negative	Positive	
Numbers	29	27	
Gestational age (weeks)			
At registration	14 (2·8)	14 (2·3)	NS
At delivery	40 (1·8)	40 (1·3)	NS
First recorded weight (kg)	53·9 (5·4)	50·9 (4·8)	$P<0{\cdot}03$
Height (cm)	156 (3·3)	156 (4·3)	NS
Body-mass index (kg/m^2)	22·4 (2·4)	20·6 (1·7)	$P<0{\cdot}02$
Predelivery weight (kg)	56·6 (6·1)	58·5 (6·0)	NS
Pregnancy weight gain (kg)	2·7 (2·0)	7·6 (2·3)	$P<0{\cdot}001$
Postpartum weight (kg)	51·3 (5·6)	53·9 (5·8)	$P<0{\cdot}08$ (NS)
Net weight gain (kg)	−2·6 (1·9)	3·1 (2·0)	$P<0{\cdot}001$
Infant birthweight (g)	3060 (325)	3300 (420)	$P<0{\cdot}02$

Results are means (SD).

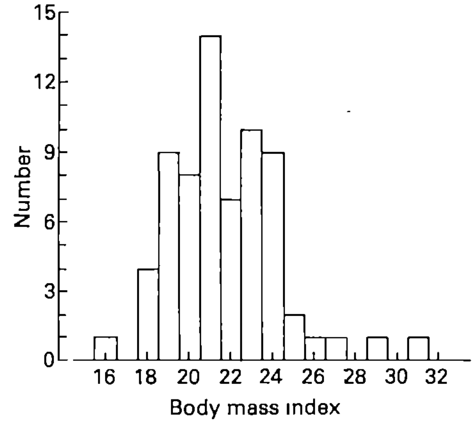

Fig. 5. Body-mass index in early pregnancy in 68 Ilula women. Underweight· <19; ideal weight. 19–22; moderately overweight: 23–28.

1985). Also, the finding in several studies that maternal food supplementation during pregnancy has a beneficial effect on these factors has generated ideas for nutritional interventions in pregnancies at risk of low-birthweight babies (Lechtig *et al.* 1975; Prentice *et al.* 1983).

Routine weighing during pregnancy has been readily accepted, as it is a very simple procedure without a need for special training. The bathroom scale generally used in health care in developing countries, and also in this study, is only exact to the kilogram Still, for longitudinal routine monitoring of weight changes during pregnancy and for the purpose of the present study, this degree of accuracy seems acceptable.

In this study the weight gain seemed to be fairly linear during pregnancy after the first trimester. This is in accordance with most reports on pregnancy weight gain based on more accurate measurements and larger series. There is no agreement as to the 'normal' range of weight in pregnancy. In developed countries a prepregnancy weight of >50 kg and a mean weight gain of 12 kg has been accepted as normal (Hytten & Leitch 1971). In comparison with these values, 20% of the Ilula women would be considered as underweight, and very few would achieve a 'normal' weight increase. On the other hand, when maternal height is also considered, as in the BMI, Ilula women do not show a very different distribution from that of Swedish women (B. Moller, unpublished data), 25% of whom have a BMI of ≤20.

A reasonable interpretation is that these women in Ilula are not in a state of acute undernutrition during the current pregnancy, but rather are uniformly stunted in growth, probably as a result of lack of adequate nutrition during childhood and adolescence and also over generations (Barron & Thomson 1983). We have no reference data for the normal height in this population.

When the weight within 48 h after delivery was compared with the weight in early pregnancy, this net weight gain was found, on average, to be nil. Thus, half the women actually lost weight during pregnancy when the weight of the products of conception was excluded. In fact, most women probably had an overall weight loss, as weight loss at this time after delivery is not yet complete.

It is interesting to note that there is generally no association between parity and maternal weight, so that these women manage to make up for the energy deficit of one pregnancy before the next one.

The relations of infant birthweight to maternal weight and weight gain were statistically highly significant in the multiple regression analysis. This analysis was not entirely satisfactory in that the weight recorded at registration was obtained at various gestational ages. For those registering late it meant that a considerable part of weight gain had already taken place and was included in the 'first' weight. As a consequence of that the relative importance of prepregnancy weight and pregnancy weight gain might be different from that obtained in this analysis, but in this study both definitely influenced birthweight. This relation was evident also when the women were grouped according to

Table 3. Multiple linear regression analysis with birthweight as the dependent variable, and the first recorded weight and pregnancy weight gain as independent variables ($n = 331$)

Predictor	Multiple regression coefficient	SE	Significance level
Constant	2230	185	
First recorded weight (mean at 23 weeks)	15	3	<0·0001
Pregnancy weight gain	26	6	<0·0001

Coefficient of determination (R^2) = 0·10 (residual standard deviation = 395)

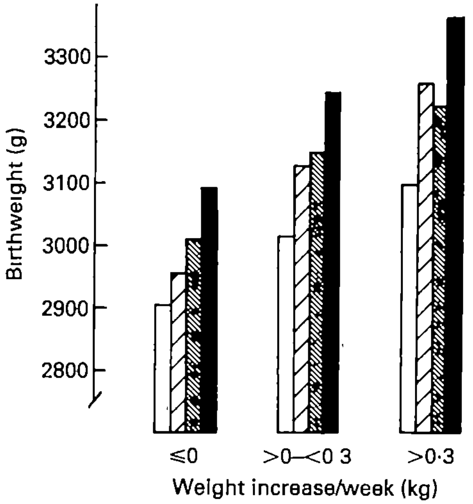

Fig. 6. Mean birthweight by maternal weight at registration to antenatal care and pregnancy weight gain ($n = 331$). First recorded weight (kg). □, ≤49; ▨, 50–54; ▩, 55–59; ■, ≥60.

their weights at registration as in Fig. 6. The contribution of pregnancy weight gain to birthweight was no less in women with a weight >60 kg than for those <50 kg. This is also what is to be expected in this range of weights where pronounced obesity is unusual (Abrams & Laros 1986).

As the maternal prepregnancy weight and weight gain have often been found to correlate positively with birthweight (Venkatachalam 1962; Gebre-Medhin *et al.* 1978), as in the present study, the low maternal weights in developing countries have naturally been put forward as a main explanation for the shift to the left of the birthweight distribution and for the high prevalence of low-birthweight babies. However, in the present study, as in most other studies, a multiple regression analysis demonstrated that only a relatively small proportion of the observed total variation in birthweight was explained by the correlation of birthweight with maternal weight and weight gain. This is also in accordance with a study in Tanzania by Bantje (1986) who found that <9% of the variation in birthweight was explained by maternal weight indices.

Kusin & Jansen (1986) used a more complex statistical model which also included parity, triceps skinfold, haematocrit and the sex of the newborn, but still could explain only 30% of the variation in birthweight. Their observation of a mean maternal weight gain of 6 kg and their findings concerning the effects of increased maternal weight and weight gain on birthweight are similar to our results. The low weight gain during pregnancy indicates a rather restricted level of energy intake when compared with the weight increase in populations where the pregnant women eat 'to appetite' and maybe also consume food of higher energy density.

There is evidence, at least in populations where the energy needs are met, that the positive relation between maternal weight and fetal growth is not explained by the maternal increase in fat mass, but rather by the amount of lean body mass present in the mother before pregnancy (Langhoff-Roos 1987). The positive association between weight increase and birthweight will then rather express the favourable effect of a more pronounced increase in blood volume and other pregnancy-induced changes in body composition. However, in the group of Ilula women for whom it was possible to calculate the net weight gain, significantly higher birthweights were found in infants of women with a positive net weight gain after delivery in spite of a lower weight in early pregnancy. Although methods for analysis of the composition of this net weight gain have not been used, it may be at least to some extent an expression of the increase in fat mass. This difference in birthweight might indicate that a positive energy balance is favourable for fetal growth in women in a suboptimal nutritional condition.

Even so, it seems difficult from this study to find support for definite recommendations of maternal nutritional supplementation The suggestion by Wray (UNICEF 1985), that all women not gaining at least 1·5 kg/month during the last 6 months gestation should be considered for nutritional supplementation, in Ilula would include 85% of all pregnant women. Most studies indicate that mean birthweight might increase around 50 g in successful supplementation programmes (Rush 1982), with better effects in semi-starved individuals. The acceptable mean term birthweight of Ilula babies may partly be due to the satisfactory nutritional status at the onset of pregnancy, as reflected in BMI, which may compensate for the relatively low pregnancy weight gain. It also should be borne in mind that for each 1000 m above sea level a reduction of 100 g in mean birthweight is to be expected (Hytten & Leitch 1971). With this compensation, the women with the best prepregnancy weight and the best pregnancy weight gain had babies with a mean birthweight in the same range as in affluent societies.

Conclusions

There was a statistically significant improvement in birthweight with better maternal weight and weight gain. An extra kilogram of maternal weight gain theoretically increased infant birthweight by only 26 g. Only a small part of the variation in birthweight was explained by maternal weight indicators. This does not mean that maternal nutrition is unimportant, only that the effects of better nutrition are not reflected in immediate and conspicuous increases in birthweights. There is much evidence that reproductive performance is improved by better long-term female nutrition and that well-being and working ability are enhanced. Thus, the case is strong for nutritional education, not only of MCH attenders but also of political leaders and other influential persons. The monitoring of maternal weight in antenatal care may help to illustrate the importance of nutrition, but it is of little help in monitoring intrauterine growth.

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Protein S and protein C levels in Chinese women during pregnancy, delivery and the puerperium

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Summary. The plasma levels of protein S and protein C related antigens were determined in a group of normal pregnant Chinese women and a group of normal non-pregnant controls, using the sandwich technique of enzyme immunoassay with commercial kits. Compared with non-pregnant controls, plasma protein S levels were significantly lower during pregnancy, labour, parturition and the early puerperium. There was no significant difference in protein S levels between pregnancy, labour and puerperium. On the other hand, maternal plasma protein C levels during pregnancy and before delivery were similar to those in controls, but a significant increase was found during the third stage of labour. This increase did not persist into the early puerperium. The observed increase in protein C level immediately after delivery in our study may represent a physiological response to counter the tendency towards venous thrombosis in the parturient women, and may help to explain the almost negligible occurrence of thromboembolism in Chinese obstetric patients.

Thromboembolism is an important complication in pregnancy, and pulmonary embolism has become the leading cause of maternal mortality in the UK (DHSS 1982). Many risk factors predispose the pregnant and parturient women to this complication, the most important being the hypercoagulable state of blood during pregnancy (Pecht & Alexander 1961), with increased levels of procoagulants and thrombin activity (Ratnoff & Holland 1959). However, this predisposition to thromboembolism is countered by the plasma anticoagulant system such as antithrombin III, protein C and protein S. Acquired and congenital deficiency of antithrombin III is now a recognized risk factor for thrombosis and coagulation disorders (Winter *et al.* 1982; Hellgren *et al.* 1983), but the roles of protein C and protein S deficiency in thromboembolic disease in pregnancy are less certain. Protein S serves as a cofactor for activated protein C in the inactivation of factors Va and VIIIa (Walker 1984). They are also involved in the inhibition of plasminogen activator inhibitors, so stimulating fibrinolysis (de Fouw *et al.* 1986). Patients deficient in either protein S (Bertina 1985) or protein C (Griffin 1984) are prone to recurrent thrombotic episodes. Changes in protein C (Mannucci & Vigano 1982) and protein S (Comp *et al.* 1986) levels in pregnancy have been reported before from Europe. In the Far East, where there is an almost negligible incidence of thromboembolism in obstetric patients (de Swiet 1985), changes in protein C and protein S levels have not been investigated.

The object of this study was to investigate the concentrations of protein C and protein S in normal healthy Chinese women during pregnancy, parturition and postpartum and compare

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these with a group of normal healthy adults as controls.

Patients and methods

This study involved a control group consisting of non-pregnant healthy hospital staff and students, and women with uncomplicated pregnancies who were managed and delivered in our hospital. Informed consent was obtained from all subjects. The study cases were divided into four groups according to the time of blood sampling. Group A consisted of 20 women at all stages of pregnancy attending our antenatal clinic. Group B consisted of 20 women in the first and second stages of labour. Group C consisted of 16 women in the third stage of labour after the umbilical cord had been clamped and divided but before delivery of the placenta. Group D consisted of 19 women in the early puerperium, between 1 and 117 h after delivery.

Blood was collected by the double syringe technique to minimize contamination. After a clean venepuncture with needle and syringe, the first 2 ml of blood were discarded, and a new syringe was substituted to collect the rest of the free flowing blood which was immediately transferred to plastic tubes containing 3·8% tri-sodium citrate in the ratio of 9 parts to 1. The tubes were placed in crushed ice immediately after collection and centrifuged at 3000 r/min for 20 min at 4°C in a Hermle ZK 364 (BHG) refrigerated centrifuge. Plasma collected was aliquoted for immediate storage at −70°C until assay. Samples were collected over a period of several months and assayed in single batches. All plasma specimens were thawed at 37°C for 15 min before assay.

Plasma protein S and protein C related antigens were measured by the sandwich technique of enzyme immunoassay (ELISA) using commercially available assay kits from Diagnostica Stago (Asnieres, France) and following manufacturer's recommendations. The solid phase (micro-ELISA plate) is coated with specific F(ab') fragments to either protein C or protein S, and enzymatic activity is obtained by using OPD (Ortho Phenyline Diamine) with hydrogen peroxide as substrate and 1 M HCl to block the reaction. Absorbance of each well was determined at 490 nm using MR600 Microplate reader (Dynatech Product). Micro-ELISA plates were purchased from Dynatech Product. Standard plasma of protein C was obtained from Diagnostica Stago, and normal plasma standardized against this was used as protein S reference.

Results

The individual values of protein S and protein C levels in all groups are shown in Figs 1 and 2 respectively. In group D, the time of blood sampling varied between 1 h and 117 h postpartum; most samples (89% and 80% for protein C and protein S respectively) were collected within 42 h of birth. The values of the later samples (73, 80 and 117 h) all fell within the range of the earlier samples.

The mean values of protein S and protein C levels in all groups were compared with the controls, with the number of available results shown in Table 1. Compared with the non-pregnant

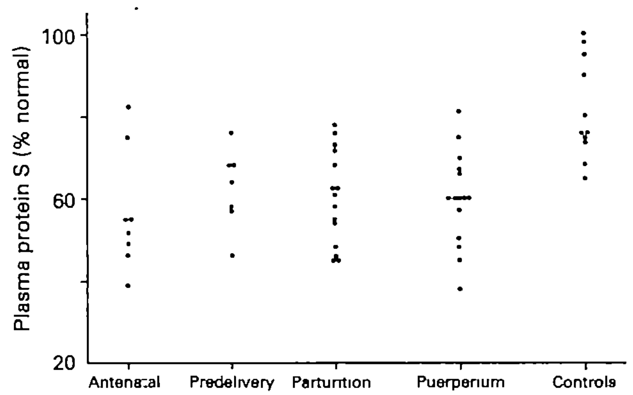

Fig. 1. Total protein S antigen levels in normal pregnant women at different stages of pregnancy and in the normal controls

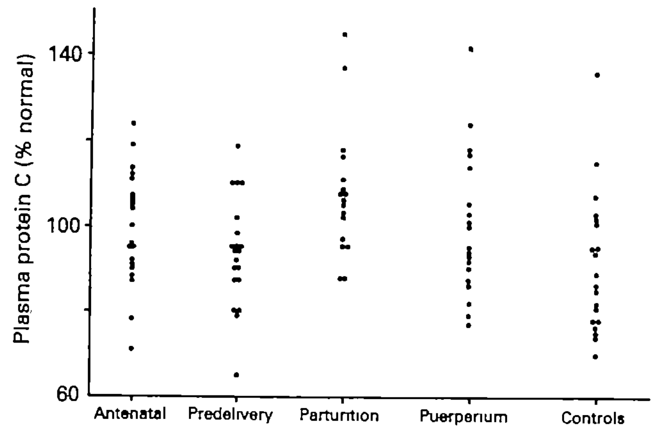

Fig. 2. Total protein C antigen levels in normal pregnant women at different stages of pregnancy and in the normal controls.

control group, the pregnant women had significantly decreased protein S levels throughout pregnancy, delivery and the early puerperium. There was no significant difference in the level of protein S between pregnancy and parturition. On the other hand, there were no significant differences in mean protein C levels compared with the control group until after the birth of the fetus when the mean protein C level was significantly higher than the mean level in the control group and also the level during labour. This increase did not persist into the early puerperium.

Discussion

Thromboembolic disease in the pregnant Chinese woman is rare, and there was no available information on the incidence of this problem in Hong Kong. A previous study of Chinese women who underwent gynaecological surgery revealed an overall rate of leg venous thrombosis, as diagnosed by a positive ^{125}I fibrinogen scan, of 2·6%, which was much lower than the rate in Europeans (Tso *et al.* 1980). In another study in Chinese patients after stroke, the total rate of deep vein thrombosis was 17% and no clinical evidence of pulmonary embolism was seen (Tso 1980). This phenomenon is thought to be related to the efficient fibrinolytic activity in non-European people (Franz *et al.* 1961) which in turn is related to diet (Gans *et al.* 1971). On the other hand, disturbance in the anticoagulant system may predispose Chinese patients to develop postoperative deep vein thrombosis, which is associated with a decrease in antithrombin III level (Tso *et al.* 1980), and the anticoagulant system may play a significant yet unrecognized role in the low incidence of thromboembolic disease in the Chinese. It is therefore of interest to examine the changes of protein S and protein C levels in pregnant healthy Chinese women.

Table 1. Levels of protein C and protein S in normal pregnancy, delivery and puerperium compared with non-pregnant controls†

Patient group	*n*	Protein C		*n*	Protein S	
Control group (non-pregnant)	20	91·1	(15·9)	11	81·5	(11·6)
A (pregnancy)	20	99·3	(13·2)	8	56	(14·2)**
B (first and second stage)	20	94·6	(12·8)	7	62·4	(9·0)*
C (third stage)	16	107·6	(14·7)*	15	60·3	(11·0)**
D (puerperium)	19	99·9	(16·4)	15	59·8	(11·0)**

Significance of differences using Student's *t*-test: protein C levels were significantly higher in group C compared with group B or the control group $P<0·01$, protein S levels were significantly lower in all groups compared with the control group *$P<0·01$, ** $P<0·001$.

†Results are mean (SD) values and are expressed as a percentage of the reference value, *n* is the number of available samples in each group.

Comp *et al.* (1986) has shown that there was a significant reduction in protein S activity throughout pregnancy and delivery and this was a result of reduced total protein S antigen. Mannucci *et al.* (1984) demonstrated a significant elevation of protein C antigen in the last two trimesters and on the fifth postpartum day. Our results support the findings of Comp *et al.* (1986) but are at variance with those of Mannucci *et al.* (1984). Although methodological difference might account for the discrepancy between our findings and those of Mannucci *et al.* (1984), we think that our observation may be explained by the hypothesis that at the time of the third stage of labour, activation of the coagulation system is accelerated, and as protein C is an important natural anticoagulant as well as a profibrinolytic agent (Griffin 1984), it may be increasingly released from the liver in response to the level of circulating activated procoagulants. The difference in our observation may also explain the low rate of thromboembolic disease in Chinese obstetric patients, as protein C level did not increase even after placental separation and on the first postpartum day in the women studied by Mannucci *et al.* (1984).

It is possible that different levels of circulating antithrombin III, protein C and protein S in Chinese pregnant women in response to delivery or surgery account for the lower frequency of thromboembolic disease in the Chinese. This interesting aspect needs to be investigated further.

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Human amniotic fluid urogastrone (epidermal growth factor) and fetal lung phospholipids

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Summary. Urogastrone was measured by radioimmunoassay in amniotic fluid obtained from 186 complicated pregnancies at 22 to 40 weeks gestation. Amniocentesis was performed for a variety of indications to obtain information about fetal lung maturity or bilirubin levels before induction of labour or caesarean section in various obstetric conditions. In 114 specimens lung phospholipids extracted from amniotic fluid were also assayed using two-dimensional thin layer chromatography. Urogastrone concentrations became measurable at approximately 30 weeks gestation and thereafter there was a 10-fold rise in concentrations between 30 and 40 weeks gestation. This increase in urogastrone concentration was positively correlated with a rise in phosphatidylcholine and phosphatidylglycerol concentrations and the phosphatidylcholine (lecithin)/sphingomyelin ratio (L/S). These results are compatible with a role for urogastrone in human fetal lung maturation.

Urogastrone, isolated from human urine, and the mitogen epidermal growth factor (EGF) are known to be similar in molecular structure (Gregory & Willshire 1975) and in chemical and biological properties (Gregory 1975; Gregory *et al* 1978). Both peptides share the same receptor sites in human tissues with approximately equal affinities (Hollenberg & Gregory 1976; Hollenberg 1979), and it is concluded that urogastrone is human EGF. The only known sources of EGF production in man are the submandibular glands (Cohen 1962) and Brunner's glands in the duodenum (Elder *et al.* 1978). Animal studies have suggested a physiological role for the peptides in fetal lung maturation in that administration of mouse EGF to fetal rabbits (Catterton *et al* 1979) and fetal lambs (Sundell *et al.* 1980) *in vivo* increased the number of lamellar bodies in type II cells and increased lung compliance. Recently we have shown that human urogastrone injected into fetal rabbits increased the phospholipid content of lung washings (Haigh *et al.* 1988). Also, enhanced phosphatidylcholine synthesis was observed in lung slices from fetal rats 2 days after intra-amniotic treatment with mouse EGF (Sundell *et al.* 1980; Warshaw *et al.* 1985). Initial in-vitro studies failed to demonstrate an action of mouse EGF alone on phospholipid synthesis in cultured lung tissue (Keller & Ladda 1981,

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Leheup *et al.* 1983). Subsequent studies have shown that mouse EGF can stimulate both choline and acetate incorporation into phosphatidylcholine in fetal rat lung explants (Keller & Ladda 1981). Human urogastrone has a similar effect, with a direct action on type II cells from fetal rabbit lung in culture (Gross *et al.* 1986; Haigh *et al.* 1988).

In previous studies the physiological role of this hormone in human fetal maturation has been assessed by measurement of its concentration in amniotic fluid. Starkey & Orth (1977) were unable to detect EGF, but Barka *et al.* (1978) measured EGF in the range 0·06 to 1·1 ng/ml at 16–24 weeks gestation, and Ladda *et al.* (1979) reported concentrations between 0·9 and 8·8 ng/ml at 16–18 weeks gestation. However, these studies were performed in early pregnancy with assays of uncertain specificity. Therefore, the object of the present study was to measure urogastrone in amniotic fluid collected in the third trimester to detect any changes which might occur with gestational age. In addition, the phospholipid content was measured in a number of these amniotic fluids as an index of fetal lung maturation in order to investigate the association of this with changes in urogastrone concentration.

Patients and methods

Amniotic fluid samples

Preterm amniotic fluid was collected by transabdominal amniocentesis for reasons of clinical management by obstetricians at St Mary's Hospital, Manchester, and at other hospitals in the North Western Region to determine fetal lung maturity by the phosphatidylcholine (lecithin)/sphingomyelin (L/S) ratio, or the severity of rhesus haemolytic disease by bilirubin measurement. The clinical indications for amniocentesis were suspected intrauterine growth retardation (IUGR), pre-eclampsia, diabetes, hypertension, or rhesus isoimmunization. In term pregnancies, fluid was obtained by amniocentesis in women undergoing elective caesarean section at 38–40 weeks gestation. The indications for caesarean section were a scarred uterus due to a previous caesarean section, cephalopelvic disproportion, breech presentation, transverse lie of the fetus, IUGR, pre-eclampsia, hypertension or diabetes. Amniotic fluid specimens were centrifuged at 140 *g* for 10 min to remove cellular debris, and the supernatant was stored at −20 °C. Preliminary studies had shown that repeated freezing and thawing did not affect phospholipid or urogastrone concentrations in amniotic fluid.

Urogastrone radioimmunoassay

Urogastrone was determined as described by Gregory *et al.* (1977) and modified to measure the lower concentrations known to occur in amniotic fluid (Wren *et al.* 1984). Aliquots of 250 μl amniotic fluid were assayed in triplicate, together with urogastrone standards and blank controls. A 250 μl sample of rabbit anti-urogastrone monoclonal antibody was added and the samples were incubated at 4 °C for 24 h followed by the addition of 250 μl of ^{125}I-labelled urogastrone. The incubation was then allowed to continue at 4 °C for 48 h; 100 μl donkey anti-rabbit precipitating serum was added and the incubation continued for a final 16 h at 4°C. The precipitate was separated by centrifugation, and counted for ^{125}I. A standard curve of specific binding was prepared, and the concentration of urogastrone in amniotic fluid was calculated as ng/ml

Phospholipid assay

Phospholipids were extracted from 1–5 ml amniotic fluid, using chloroform-methanol (2:1; v:v) as described by Folch *et al.* (1957). Extracted phospholipids were separated by two-dimensional thin layer chromatography (James *et al.* 1984). The amounts of each phospholipid were determined by phosphorus assay using the malachite green reagent (Anner & Moosmayer 1975). The concentration of phospholipid was expressed as μg phospholipid/ml of amniotic fluid The L/S ratio was calculated from the phosphatidylcholine and sphingomyelin concentrations in amniotic fluid.

Materials

Recombinant human urogastrone was provided by G. D. Searle and ICI (Pharmaceuticals Division) and was of a high standard of purity (Franklin *et al.* 1986). Antibody to urogastrone was a gift of ICI plc. Donkey anti-rabbit precipitating serum was obtained from Wellcome Reagents Ltd, Beckenham, Kent. Na ^{125}I (13–17 mCi/μg) used in the preparation of ^{125}I-labelled urogastrone was from Amersham International plc, Amersham, Bucks; 'iodo-gen' was from Pierce & Warringer (UK) Ltd, Chester, Cheshire; and Biogel P6 was from Bio-Rad Laboratories Ltd, Watford, Herts. All other reagents were of ANALAR grade supplied by BDH Chemicals Ltd, Poole, Dorset.

Statistics

Mean values were compared by a two-tailed Students's *t*-test. Since there were large differences in gestational age at amniotic fluid sampling between diagnostic groups a possible effect of the different obstetric conditions on amniotic fluid urogastrone concentration was evaluated using a binomial logit model:

$$\mathrm{Log}_e\left(\frac{P}{1-P}\right) = DG+b_1\ GA+b_0$$

(where DG = diagnostic group, GA = gestational age, and b_1 and b_0 are maximum likelihood estimates). This model relates the probability (P) of being able to detect urogastrone ($\geq$0·1 ng/ml) to both gestational age and diagnostic group. When calculated, the model has a deviance which changes if either the term 'diagnostic group' or 'gestational age' is dropped. The change in the deviance is distributed as a χ^2 variable.

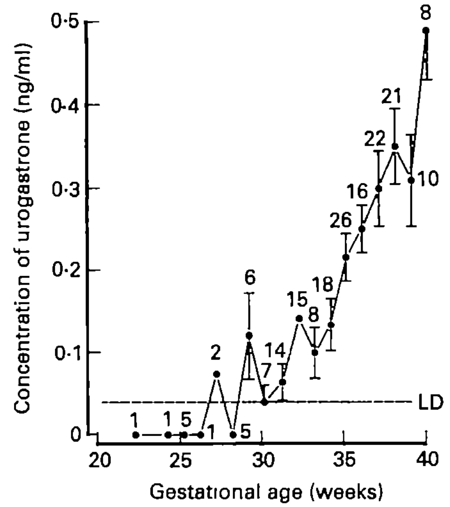

Fig. 1. Changes in amniotic fluid urogastrone concentrations with increasing gestational age. Each experimental point is the mean±SEM of the number of values shown LD, Lower limit of detection. Urogastrone concentrations at 30 weeks *vs* urogastrone concentrations at 40 weeks gestation. $P<0{\cdot}001$

To investigate further a possible association between urogastrone concentration and gestational age the results were $\log_{10}$ transformed, plotted against gestational age, and lines of regression drawn for each diagnostic group. Using one-way analysis of variance, differences between regression lines for each diagnostic group were evaluated. Finally, the urogastrone data were $\log_e$ transformed and weighted by adding a constant value of 0·15, and plotted against gestational age. Analysis of variance was carried out on the regression lines for each diagnostic group.

The correlation coefficient (r) for urogastrone *vs* L/S ratio, and concentrations of various types of phospholipids was calculated and the significance of r was calculated by a *t*-test.

Results

Amniotic fluid urogastrone

A single amniotic fluid sample was collected from each of 186 women between 22 and 40 weeks gestation. The lower limit of sensitivity for urogastrone detection was 40 pg/ml. Figure 1 shows the mean amniotic fluid urogastrone concentration in relation to gestational age. The concentration rose steadily with increasing gestational age, the rate of increase being approximately constant after 30 weeks gestation. The mean urogastrone concentration at 40 weeks gestation was more than 10 times greater than that at 30 weeks.

Amniotic fluid urogastrone and obstetric conditions

Tables 1 and 2 show the numbers of amniotic fluid samples collected in various obstetric conditions and the urogastrone concentrations respectively. Using the binomial logit model the probability of being able to detect urogastrone in amniotic fluid is dependent on gestational age and not diagnostic group. In Figure 2, analysis of variance showed no significant differences between the lines of regression for diagnostic groups. Similar analysis in which the data were $\log_e$ transformed and weighted again showed no significant differences between diagnostic groups. Further, a comparison of the mean urogastrone concentrations in Table 2 shows sig-

Table 1. No. of amniotic fluid samples obtained in various obstetric conditions and assayed for urogastrone (U) and phospholipids (P)

	No. of amniotic fluid samples obtained at gestational age (weeks)									
	≤30		31–33		34–36		37–40		Total	
Obstetric condition	U	P	U	P	U	P	U	P	U	P
Pre-eclampsia	1	0	2	2	8	7	6	6	17	15
Diabetes	1	0	1	1	14	8	13	10	29	19
Hypertension	2	2	7	2	7	5	3	3	19	12
Suspected IUGR	1	0	4	3	8	4	5	1	18	8
Rhesus	18	9	20	14	15	8	3	0	56	31
Others*	4	0	3	1	9	5	31	23	47	29
Total	27	11	37	23	61	37	61	43	186	114

* This group includes the following conditions: scarred uterus due to previous section, transverse lie, cephalopelvic disproportion and breech presentation.

U, Urogastrone assay; P, phospholipid assay.

nificant differences (*t*-test) between gestational age subgroups but not by diagnostic group. Since these obstetric conditions had no significant effect on amniotic fluid urogastrone concentration the data were pooled to produce Fig. 1.

Amniotic fluid urogastrone and fetal lung maturation

After assaying for urogastrone the remaining amniotic fluid was used to determine the phospholipid content. Unfortunately, the amount of fluid available was sufficient for phospholipid measurement in only about two-thirds ($n = 114$) of the total number of samples (Table 1). Figure 3 shows the concentration of various phospholipids in three gestational age subgroups, 31–33 weeks, 34–36 weeks, and 37–40 weeks. In this 10-week period the concentration of sphingomyelin remained approximately constant but those of phosphatidylinositol, phosphatidylcholine and phosphatidylglycerol increased with gestation. The data illustrated in

Table 2. Urogastrone concentrations in amniotic fluid obtained in various obstetric conditions in four gestational age subgroups

	Amniotic fluid urogastrone (ng/ml) at gestational age (weeks)			
Obstetric condition	≤30	31–33	34–36	37–40
Pre-eclampsia	0·10 ($n = 1$)	0·16, 0·18 ($n = 2$)	0·14 (0·06) ($n = 8$)	0·23 (0·07) ($n = 6$)
Diabetes	0·14 ($n = 1$)	0·07 ($n = 1$)	0·26 (0·09) ($n = 14$)	0·24 (0·08) ($n = 13$)
Hypertension	0·15, 0·08 ($n = 2$)	0·13 (0·11)* ($n = 7$)	0·22 (0·07) ($n = 7$)	0·51 (0·14) ($n = 3$)
Suspected IUGR	0·0 ($n = 1$)	0·05 (0·04)* ($n = 4$)	0·27 (0·09) ($n = 8$)	0·39 (0·10) ($n = 5$)
Rhesus	0·04 (0·02)** ($n = 18$)	0·10 (0·02)* ($n = 20$)	0·12 (0·02) ($n = 15$)	0·27 (0·08) ($n = 3$)
Others	0·0 ($n = 4$)	0·05 (0·02)*** ($n = 3$)	0·19 (0·04) ($n = 9$)	0·38 (0·03) ($n = 31$)

Levels of significance compared with gestational age subgroup 37–40 weeks *$P<0·05$, **$P<0·01$, ***$P<0·001$.

No significant differences between diagnostic groups.

Results are mean (SE) values, n is the number of samples assayed.

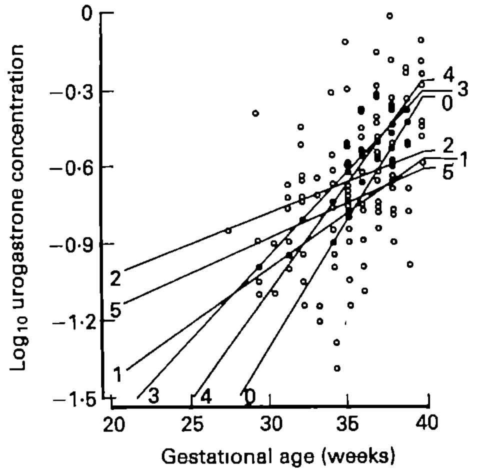

Fig. 2. The relation between $\log_{10}$ (urogastrone) and gestational age. Regression lines drawn are for the following diagnostic groups: 1, pre-eclampsia; 2, diabetes; 3, hypertension; 4, IUGR; 5, rhesus isoimmunization; 0, others (see Table 2)

Fig. 3 suggest that the increases in urogastrone are associated with increases in phospholipid in the third trimester of pregnancy. Table 3 shows that there was a relatively small but highly significant correlation between urogastrone concentration and L/S ratio, phosphatidylcholine and phosphatidylglycerol.

Discussion

Previous animal studies have suggested that EGF plays a role in fetal lung maturation (Catterton *et al.* 1979; Sundell *et al.* 1980; Gross *et al.* 1986; Haigh *et al.* 1988), and our findings lend support to a similar role for urogastrone. Amniotic fluid urogastrone increased during the third trimester alongside an increase in lung phospholipid concentrations and there was a significant relation between urogastrone and both phosphatidylcholine concentration and the L/S ratio. The amniotic fluid samples available to us came from pregnancies where there had been various obstetric indications for induction of labour or caesarean section, which are known to accelerate or retard fetal lung maturation (Tsao & Zachman 1982). We have considered any possible effects the clinical conditions might have had on the changes in urogastrone concentrations. The non-significant differences found in Table 1 cannot be taken as proof that the diagnostic groups do not differ as the numbers in each group are relatively small, it appeared that the rise in urogastrone concentration was predominantly gestational age related.

The association between urogastrone and lung phospholipids might be coincidental since they are both related to gestational age (Fig. 3). If the relation is causal, with a higher fetal plasma urogastrone level leading to a greater release of phosphatidylcholine by type II cells, as can be demonstrated *in vitro* (Haigh *et al.* 1988), the amniotic fluid urogastrone is presumably derived from the fetal kidney (D'Souza *et al.* 1985). The alternative additional derivation from lung liquid appears improbable because of the impermeability of fetal lung epithelium to molecules of this size in the sheep (Strang 1977), and because urogastrone is not detectable in pharyngeal secretions after birth (S. W. D'Souza, unpublished observations). More detailed speculation would require knowledge of the antenatal urinary clearance of urogastrone and its half-life in amniotic fluid, neither of which is known.

Evans *et al.* (1986) measured urinary urogastrone excretion in newborn infants and found a twofold higher level in term than in preterm infants at birth. The mean urinary urogastrone concentration was 18·2 ng/mg creatinine in infants born at <32 weeks gestation and 34·3 ng/mg creatinine in those born at >37 weeks gestation, an increase of 88%. The estimated increase in amniotic fluid concentrations calculated from our data and the data of amniotic fluid creatinine published by Lind *et al.* (1971) was 275% from 0·04 ng to 0·15 ng urogastrone/mg creatinine in the same gestational period. The increase in the urogastrone/creatinine ratio with gestation is greater in amniotic fluid than in urine but the absolute ratios are much lower in amniotic fluid at all gestations. Since amniotic fluid creatinine concentrations increase with gestational age the rise in the urogastrone/creatinine ratios suggests an increased production of urogastrone during gestation rather than an increase due to greater fetal kidney output. It is known that EGF binds to specific cell receptors, the complex formed with receptors is internalized in cells and degraded in lysosomes (Carpenter & Cohen 1976). Therefore, a possible explanation for the lower ratio in amniotic fluid is hormonal-binding locally to receptors in fetal and placental tissues which are

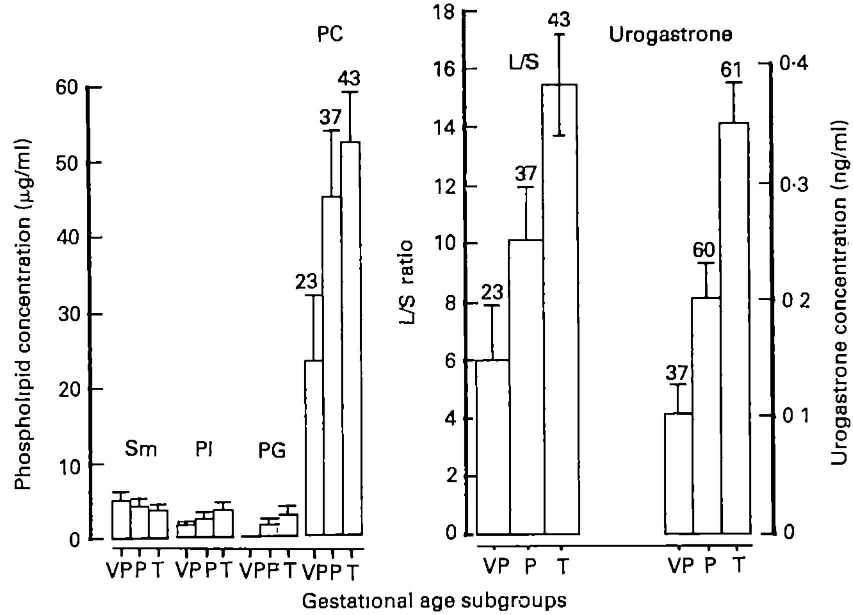

Fig. 3. Mean amniotic fluid concentrations of phospholipids, the L/S ratios and urogastrone in three gestational age subgroups: VP (very premature, 31–33 weeks), P (premature, 34–36 weeks) and T (term, 37–40 weeks). Sm, Sphingomyelin, PI, phosphatidylinositol; PG, phosphatidylglycerol, PC, phosphatidylcholine; L/S, lecithin/sphingomyelin ratio. Results are means±SE of the numbers (*n*) shown *n* values for Sm, PI and PG subgroups are similar to those shown for PC. Levels of significance: L/S ratio VP *vs* P, NS; P *vs* T, $P<0{\cdot}05$; VP *vs* T, $P<0{\cdot}001$. Urogastrone: VP *vs* P, $P<0{\cdot}001$; P *vs* T, $P<0{\cdot}001$; VP *vs* T, $P<0{\cdot}001$. PC: VP *vs* P, NS; P *vs* T, NS; VP *vs* T, $P<0{\cdot}01$. PG: P *vs* T, $P<0{\cdot}05$. PI: VP *vs* P, NS; P *vs* T, NS; VP *vs* T, $P<0{\cdot}01$. Sm VP *vs* P, NS; P *vs* T, NS; VP *vs* T, NS.

known to be rich in EGF receptors (Thorburn *et al.* 1981). Urogastrone at these low concentrations in amniotic fluid and in urine has been shown to be biologically active in cell culture studies (Haigh *et al.* 1988).

The appearance of urogastrone in amniotic fluid in our study coincides with the appearance of fetal lung type II cells previously reported by other authors (Perelman *et al.* 1981; Hallman 1984). The developmental increase in urogastrone might reflect the increased numbers of type II cells with lamellar bodies (Perelman *et al.* 1981). Further, the developmental increase in urogastrone seems to coincide with an increase in fetal compartments of thyroid hormones and glucocorticoids (Ballard 1982), both of which can accelerate fetal lung maturation. In an earlier study (D'Souza *et al.* 1985), a positive relation was found between amniotic fluid urogastrone concentration at term and placental weight, implying a possible role in promoting placental growth in human pregnancy.

Table 3. Coefficients of correlation between urogastrone and phospholipid concentrations in amniotic fluid

Relation	*r*	*n*	*P*
URO *vs* L/S	0·349	96	<0·001
URO *vs* PC	0·271	96	<0·01
URO *vs* PG	0·352	96	<0·001
URO *vs* PI	0·068	96	NS
URO *vs* Sm	0·072	96	NS

URO, Urogastrone; L/S, lecithin/sphingomyelin ratio; PC, phosphatidylcholine; PG, phosphatidylglycerol; PI, phosphatidylinositol; Sm, sphingomyelin.

Many obstetric units are no longer carrying out routine analysis of amniotic fluid for fetal lung maturity when the indication for induction of labour cannot be avoided, as in fulminating pre-eclampsia; while in others, such as diabetes mellitus, early induction is no longer a feature of obstetric management. Indeed, in such pregnancies relatively few amniotic fluid specimens were obtained for us at gestational ages <34 weeks (Table 1). It is doubtful from the results of the present study whether amniotic fluid urogastrone measurement has immediate clinical application. Firstly, the time involved in the assay (88 h in our study) could prejudice its usefulness for assessing fetal lung maturity since clinical action would be delayed. Secondly, the weak correlations between urogastrone and phosphatidylcholine levels, or the L/S ratio, raise uncertainty about whether urogastrone measurements would replace established investigations for fetal lung maturity. This can be further studied by collecting amniotic fluid specimens at birth in preterm deliveries in order to investigate the relation of urogastrone levels to clinical outcome, including the frequency of respiratory distress in newborn infants.

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Tocolysis during cervical ripening with vaginal PGE$_2$

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Summary. Forty-two primigravidae with unripe cervices (modified Bishop score ≤ 5) were pretreated with 8 mg of oral salbutamol 30 min before vaginal administration of 5 mg of PGE$_2$. The proportion of patients in established labour after treatment (19%) was markedly less than results reported previously and cervical improvement occurred in 86% of the non-labouring patients. The improved outcome of labour associated with the prior administration of PGE$_2$ when the cervix is unripe, including reduced induction-to-delivery intervals and higher rates of vaginal delivery was maintained. Apart from some minor side-effects, there were no adverse effects noted as a direct consequence of the tocolytic; blood loss was not increased, although one patient suffered an intrapartum abruption. This approach allows a greater control of induced uterine activity and timing of delivery which may be of particular importance in women with suspected placental insufficiency.

It is recognized that the prospects following induced labour when the cervix is unripe are compromised for both mother and fetus. The local administration of prostaglandin E$_2$ (PGE$_2$) immediately before a planned labour induction has been shown to improve cervical favourability and enhance the outcome of labour by shortening induction–delivery intervals, reducing the need for caesarean section for failed inductions, and to decrease the number of babies born with low Apgar scores (Calder *et al.* 1977; MacKenzie & Embrey 1977).

The ripening process appears to take more than 15 h in some patients, and in up to 60% may result in the initiation of labour at a time when the delivery unit is unprepared to receive the patient. This is of particular importance if problems are anticipated with the labour, especially fetal distress due to placental dysfunction. The concept of suppressing the uterine activity stimulated by the prostaglandins, and thus preventing labour ensuing before the planned induction, has been explored using simultaneous β-sympatho-mimetic administration.

Patients and methods

Forty-two primigravidae with singleton pregnancies and fetal vertex presentation at 38–43 weeks gestation (mean 40·6, SD 1·4 weeks) scheduled for labour induction were studied with their consent. The primary indications for induction were hypertensive conditions in 13, post-term in 26, placental insufficiency in one and maternal discomfort or large baby in the remaining two women. In each instance a cervical assessment was performed and the women were recruited if the modified Bishop score was ≤ 5. At 1800 hours approximately, 8 mg of salbutamol were given orally, followed 30 min later by a 5-mg PGE$_2$ witepsol vaginal pessary (MacKenzie *et al.* 1981). Maternal pulse and occurrence of symptoms including nausea, vomiting,

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dyspnoea, tremor, and uterine cramps, and the fetal heart rate and pattern were recorded by external tocography for the subsequent 3 h.

The following morning at 0900 hours, the cervix was assessed again by the same observer without reference to the initial cervical score and a low amniotomy was performed: a titrated intravenous infusion of oxytocin at 2 mU/min was started 1 h later, increasing to a maximum of 48 mU/min as necessary. Subsequent intrapartum management was directed by the duty delivery-suite staff.

Results

Characteristics of labour outcome are shown in Table 1. In none of the 42 patients was there any evidence of a complication developing as a result of the salbutamol administration. Ten (24%) patients experienced some tremor for approximately 30 min starting 15–30 min after salbutamol treatment, and 13 (31%) had a tachycardia of 100–120 beats/min for up to 2 h after therapy; in none was this distressing. No patients had any nausea or vomiting during the ripening procedure before the onset of labour. Uterine tightenings were felt by the patient or observed on the tocograph (used in 31 women) in 32 women (76%): 8 (19%) established labour before the planned amniotomy (Table 2). In one of these patients, labour commenced during the first 3 h after PGE$_2$ administration when there was evidence of fetal distress on the cardiotocograph and clinical signs of placental abruption: an immediate caesarean section was performed 4 h after pessary insertion when a 200-ml retroplacental haematoma was found. The newborn infant was in good condition at delivery and made excellent subsequent progress.

Table 2 lists the proportion of patients with changes in cervical score at the time of formal amniotomy the following morning. In the 34 women not in labour, the mean cervical score increased from 3·9 (SD 1·1) to 6·6 (SD 1·9) (P<0·0001, Student's paired t-test). There was no relation between cervical response to the prostaglandins and the occurrence of salbutamol-induced side-effects or development of uterine contractions as assessed by the patient or the tocograph. Of 10 patients in whom uterine contractions were not detected after PGE$_2$ treatment, one had no improvement in cervical state, two improved by one point and the other seven improved by two or more points.

The duration of the first stage of labour, whether it started after prostaglandin instillation or after formal induction, did not appear to be influenced by the state of the cervix assessed at entry into the study. In one patient with placental insufficiency, the cervical score was 3 both before treatment and at the next assessment the following morning, and efforts to induce labour failed. The decision to induce was reconsidered and repeated 6 days later: on this occasion induction was successful but delivery by caesarean section was required for fetal distress at 6 cm dilatation. Four other patients required delivery by caesarean section (Table 2), in two it was for failure to obtain progressive labour beyond 5 cm cervical dilatation after 16·8 and 16·5 h of labour respectively, and in one it was for cephalopelvic disproportion at full dilatation after 12 h labour; in none of the three were there any complications for mother or baby. The last caesarean section was for the suspected abruption already mentioned.

Mean blood loss at delivery for all 42 patients was 306 (SD 193) ml. Only two patients delivered vaginally sustained a blood loss of >500 ml and in neither was there any uterine hypotonia. Hypotonia did not occur in any of the

Table 1. Details of labour outcome in 42 women

	Mean	(SD)	Range
PGE$_2$–amniotomy interval (h)*	14·7	(3·8)	3·8–23·2
PGE$_2$–delivery interval (h)*	22·0	(7·8)	5·2–36·8
Amniotomy–delivery interval (h)	9·7	(5·2)	1·3–20·3
Duration of first stage labour (h)	6·9	(3·4)	0·8–16·8
Duration of second stage labour (h)	1·9	(0·8)	0·1– 3·2
Maximum oxytocin infusion rate (mU/min)†	24	(11)	2–48

* Patient with deferred induction excluded.

† Only patients requiring oxytocin analysed.

Table 2. Relation between cervical score before therapy and changes in score, onset of labour, and caesarean section

	Cervical score before therapy		
	<3	4	5
No. of women	11	16	15
Increase in score Mean (SD)	2·6 (1·9)	3·0 (1·7)	2·3 (1·6)
No change in score	2 (18%)	1 (6%)	2 (13%)
Established labour	1 (9%)	3 (19%)	4 (27%)
Caesarean section	1 (9%)	2 (12%)	2 (13%)

patients delivered by caesarean section, and none was transfused.

For all the newborn infants, the mean birthweight was 3269 (SD 670, range 2020–4280) g, the mean 1- and 5-min Apgar scores were 7·8 (SD 1·8) and 9·9 (SD 0·3) respectively, the mean cord vein pH was 7·28 (SD 0·11) and the mean cord artery pH was 7·20 (SD 0·15). Only two infants had low 1-min Apgar scores (3 and 4 respectively), one was born by rotational forceps after a PGE_2-induced labour lasting 6·8 h and the other was born after formal induction, a first stage of 5 h and spontaneous vertex delivery. The infants had 5-min Apgar scores of 9 and 10 respectively and had uncomplicated subsequent neonatal progress. All the other newborns progressed without problems before discharge.

Discussion

The precise mechanism whereby the prostaglandins achieve a ripening of the unfavourable human cervix is unclear. There is evidence in ovine and rat studies that PGE_2 has a direct effect upon cervical softness and dilatation and this can be achieved without any contributory myometrial contractility (Ledger *et al.* 1985; Hollingsworth & Gallimore 1981). Similar incontrovertible conclusions have not been obtained in women, although it seems that cervical effacement and dilatation may occur after the local application of prostaglandins with little or no evidence of myometrial contractions.

Using intrauterine pressure catheter recordings, tocolytic agents have been shown to suppress prostaglandin-induced uterine contractions (McLean & MacKenzie 1980) and they are given in clinical practice to stop preterm labour (Karlsson *et al* 1980). They have been used for the acute management of uterine overstimulation subsequent to PGE_2 administration, to treat fetal distress with good effect allowing labour to continue (Shepherd *et al.* 1981). Goeschen *et al.* (1985) showed that cervical ripening could occur after the endocervical application of PGE_2 gel covered by β-agonist administration and they concluded uterine contractions had not occurred. However, their observations were made using external monitoring of uterine activity as in the present study, and this approach may be too insensitive to detect minor changes in contractility. We did not find that uterine contractions were abolished in most subjects but progressive labour was suppressed. Previous experience from this department indicates that between 30 and 50% of primigravidae with a cervical score of ≤3 will labour after vaginal PGE_2 treatment and 40–70% of those with a score of 4 or 5 (MacKenzie & Embrey 1978). In the present study, significantly fewer (only 19%) commenced labour after PGE_2.

As a means of ripening the unfavourable cervix and improving the outcome of induced labour, the vaginal administration of PGE_2 provides results as good as any technique reported previously. The administration of the tocolytic did not appear to have reduced the ripening effect of vaginal prostaglandins as changes in cervical favourability were found at reassessment in 26 of the 31 women who were not in labour, including 7 of 10 who had no detectable uterine contractions. These results lend subjective support to the observations reported by Goeschen *et al.* (1985).

Using the protocol described, the salbutamol allowed the PGE_2 to ripen the cervix in most of the women while preventing labour establishing before the planned induction. This approach can have particular advantages in patients with suspected placental insufficiency and an unripe cervix. Some minor side-effects resulted but these were minimal and were not distressing to any patient. We have some concern about the patient who developed a placental abruption; uterine hypotonia is a potential complication of tocolysis and could have been a consequence of therapy. We are, however, reassured that there were no patients in whom hypotonia was suspected.

Elucidation of the true benefit of this approach to labour induction requires more investigation. The concomitant measurement of uterine activity using an intrauterine pressure catheter transabdominally would provide the necessary information but would not be acceptable to most women. Randomized placebo-controlled trials will be needed therefore to demonstrate objectively the value of the concomitant administration of a tocolytic agent during cervical ripening with prostaglandins. If the benefits are confirmed, the advantages, especially in women with unsuspected and suspected placental insufficiency, will be considerable, allowing induction with added safety and enhanced prospects of achieving a vaginal delivery.

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Vaginal pH in pregnancy in women delivered at and before term

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Summary. A microelectrode was used to measure vaginal pH in a longitudinal study during pregnancy in 30 women, 28 of whom were delivered at term. Excluding pH readings made in the presence of pathogenic organisms, 120 readings were taken. The mean vaginal pH of all subjects was 4·16 (SD 0·41). Analysis of variance showed no significant within-subject variation of pH during pregnancy. Two women had spontaneous preterm deliveries (<37 weeks) and their mean vaginal pH during pregnancy was 5·05 and 5·06. Eight women admitted in preterm labour, who then gave birth, had a mean pH of 5·43 (SD 0·94) which was significantly higher than the mean pH of 10 women in labour at term (4·58, SD 0·59). The relation between bacterial growth *in vitro* and the surrounding pH was also examined. *Escherichia coli*, a potential pathogen, behaved differently from both *Lactobacillus* (a commensal organism) and *Candida albicans*. The clinical observations show a trend towards higher vaginal pH values in association with preterm labour.

Preterm labour is known to be associated with abnormal bacterial colonization of the vagina (Rush *et al.* 1976; Lamont *et al.* 1986). It has been shown that filtrates from pathogenic bacteria increase arachidonic acid metabolism by amnion cells in monolayer culture (Bennett *et al.* 1987), and that this increase in metabolism is due to enhanced phospholipase activity (P. R. Bennett, personal communication). The ratio of cyclo-oxygenase to lipoxygenase products is increased; in particular there is a significant dose-dependent increase in prostaglandin E_2 (PGE_2) production (Bennett *et al.* 1987). This increase is enhanced by the products of leucocytes, the nature of which awaits further investigation. Filtrates from lactobacilli, on the other hand, do not alter arachidonic acid metabolism.

Alteration in the vaginal flora in favour of increased numbers of pathogens will tend to increase the numbers of leucocytes present. Both these events could increase PGE_2 production by intrauterine tissues such as amnion, and this in turn may cause cervical softening and effacement as well as being a trigger for myometrial contractions.

Factors which could influence vaginal flora include vaginal pH. It has been suggested that lactobacilli acting on glycogen as a substrate produce lactic acid (Hurley *et al.* 1974) thereby helping to maintain a low vaginal pH and inhibiting the growth of pathogens (Eschenbach 1983). An increase in vaginal pH could therefore increase

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the presence of pathogens, increasing the production of PGE_2 and the likelihood of rupture of the membranes (Minkoff *et al.* 1984).

If we are to link vaginal pH with increased growth of bacterial pathogens and thence preterm labour, it is important to determine the mean and range of vaginal pH during normal pregnancy. The studies of vaginal pH in normal pregnancy have been cross-sectional (Minkoff *et al.* 1987; Singer 1975), but it is important to know the range within individual pregnancies as well as the range between subjects. The relation between vaginal pH and bacterial growth is poorly understood. In extreme cases pH will alter bacterial growth, but does bacterial growth in turn alter the surrounding pH?

The object of this longitudinal study was to determine the mean value of vaginal pH during normal pregnancies and those ending in preterm delivery. In a further cross-sectional pilot study vaginal pH was measured during early preterm and term labour. The questions of whether bacterial growth alters the pH of the surrounding medium, and what the effect of pH on bacterial growth is, were also examined *in vitro*.

Patients and methods

Clinical study

Thirty-five women with singleton pregnancies but otherwise unselected enrolled in the longitudinal study at their first visit to the antenatal clinic; informed consent was obtained. Five women subsequently miscarried. During the remaining 30 pregnancies a total of 146 vaginal pH measurements were made at intervals of 4–6 weeks by the same person.

A sterile speculum without lubrication was used to expose the cervix and posterior vaginal fornix. A high vaginal swab was taken from the posterior fornix, placed in Amie's medium, and cultured for bacterial growth. A Gallenkamp glass microelectrode pH meter was gently applied to the vaginal mucosa at the highest point of the posterior fornix. This gave a digital recording of pH accurate to two decimal places. The mean pH of three separate applications of the electrode was used for each pH recording. The range of these individual pH measurements was always within 0·3

Between recordings the electrode was cleaned and placed in a pH 7 buffer solution. The calibration was checked after every recording.

Patients with infection have been shown to have higher vaginal pH values (Peeters *et al.* 1972), so that if the high vaginal swab revealed any infection, that pH value was excluded from the profile for normal pregnancy.

Two women were delivered preterm at 35 and 35·5 weeks gestation respectively. Six pH values recorded in these women have also been excluded from the normal range.

This left 120 values obtained from 28 patients which constituted the data for determining the normal pattern. The median gestational age at delivery in this group was 39 weeks and 5 days. A mean pH value for the whole of pregnancy was calculated for each patient and these values were used to determine the mean and range of pH in normal pregnancy for the whole group. Similarly, a mean pH value was calculated for each patient during three stages of the pregnancy: 10–24 weeks, 25–36 weeks and 37–42 weeks. These mean values were used to calculate an overall mean value for early, middle and late pregnancy.

A further 12 women each had a single vaginal pH measurement during the early stages of preterm labour when the membranes were still intact, there was no vaginal bleeding, and before they had been examined digitally. These values were compared with those obtained from 10 women recorded during early spontaneous labour at term, also with intact membranes. In all subjects a high vaginal swab obtained at the time of pH measurement was sterile.

Bacterial cultures

Three organisms were studied *in vitro*: (i) *Escherichia coli*, being a relatively common vaginal pathogen; (ii) *Candida albicans* because it is a frequent cause of vaginitis in pregnancy but does not appear to cause preterm labour; and (iii) *Lactobacillus* because of its reputed role of maintaining acid vaginal pH and inhibiting the growth of pathogens.

E. coli were cultured in tryptone soya broth, *C. albicans* in Sabouraud's medium, and *Lactobacillus* in tomato juice agar.

Three different pH values were selected for the culture media for each organism, ranging from extremely acid to neutral or near neutral. These were approximately pH 7, 5 and 3 for *E. coli*, and pH 6, 4 and 2 for *Lactobacillus* and *C albicans*.

The various pH-adjusted media were inoculated with 0·5 ml of bacteria from the appropriate culture suspension and a count of viable bacteria taken for each medium. This involved serial dilution of an aliquot of the bacterial suspension, incubation of each dilution for 24 h on solid media and a count of colonies at the lowest dilution at which these were easily distinguishable (Miles *et al.* 1938). The pH-adjusted media were incubated for 24 h at 37°C and the viable bacteria were counted again using the same serial dilution technique. The pH of a sample of the filtered media was also measured after 24 h of incubation.

Results

Table 1 shows the mean vaginal pH value according to gestation. Analysis of variance within each patient shows a borderline effect of the stage of pregnancy on pH, but this was not significant (P=0·08).

Calculating a mean pH value for each patient gave an overall mean value for the whole group during normal pregnancy of 4·16 (SD 0·41). The mean pH values were distributed normally about this mean value, and had a median value of 4·05.

Preterm labour

Three pH values were obtained during pregnancy in each of two women who were subsequently delivered preterm. The mean pH values for these two women were 5·05 and 5·06. Nineteen pH values were recorded in four women who had had a previous preterm birth for no obvious reason. All four carried the present pregnancy to term. Their mean vaginal pH was 4·66 (SD 0·72) which is not significantly different from the normal mean.

A vaginal pH was measured during early term labour in 10 women in whom the membranes were intact, there was no bleeding or evidence of infection and no vaginal examination had been performed. In this group the mean pH was 4·58 (SD 0·59).

Table 1. Mean vaginal pH according to gestation

Gestation (weeks)	pH Mean (SD)
10–24	4·23 (0·57)
25–36	4·16 (0·36)
37–42	4·09 (0·52)

Similar vaginal pH measurements were made in 12 women who were admitted in early preterm labour and their mean pH was 5·17 (SD 0·87). Of these 12 women, eight were delivered as a result of this episode of preterm labour, all between 24 weeks and 35 weeks gestation (median gestation 32 weeks and 6 days) and their mean pH value was 5·43 (SD 0·94); this is significantly higher than that found in normal labour (P=0·04, unpaired t-test). In the other four (median gestation 31 weeks and 3 days), the labour was halted using beta-mimetic drugs and in those the mean pH value was 4·68 (SD 0·42) which is higher but not significantly different from that found in normal labour at term. Both of these groups had been treated in the same manner with tocolytic drugs.

Cultures

Table 2 shows the pH in culture medium before and 24 h after incubation with the three organisms: *Lactobacillus, E. coli* and *C. albicans*. The bacterial counts before and after incubation were recorded. There was no growth of any of the three organisms at the lowest pH, namely 2 or 3. There was a large increase in the number of lactobacilli and *C. albicans* during the 24 h incubation at the highest initial pH (6·1 and 5·7 respectively) with a concurrent reduction in the pH of the medium to 4·1 and 4·0 respectively at the end of 24 h. With *E. coli* there was a significant increase in numbers of bacteria at pH 5 and 7·3, with only a small reduction in pH of the medium. At the intermediate pH both *C. albicans* and *E. coli* grew well with minimal pH change of the medium while the lactobacilli did not proliferate.

The relation between the initial pH of the medium and the percentage increase in viable bacterial count after 24 h incubation, and the change in pH of the medium during the 24 h incubation period related to the increase in number of organisms is shown in Table 2.

Discussion

The contribution of preterm delivery to perinatal mortality and morbidity is high (Hull 1977). Recent work has focused on possible causal factors associating vaginal infection and preterm delivery (Lamont *et al.* 1985). It is

Table 2. Change in medium pH and bacterial count after 24 h incubation

	Initial pH	Final pH	Per cent fall in pH	Increase in viable bacterial count
Lactobacillus	2·0	2·0	0	0
	4·0	4·0	0	0
	6·1	4·1	33	$1{\cdot}3\times10^4$
C. albicans	2·0	2·0	0	0
	3·5	3·4	3	$8{\cdot}6\times10^2$
	5·7	4·0	28	$5{\cdot}5\times10^4$
E. coli	3·0	3·0	0	0
	5·0	4·4	12	$6{\cdot}3\times10^3$
	7·3	6·9	5·5	$1{\cdot}4\times10^4$

thought that the prevalence of lactobacilli increases as pregnancy progresses, and an inverse relation between the concentration of lactobaccilli and other bacteria has been shown (Paavonen 1983). The increased concentration of lactobacilli has been linked to the increased lactic acid content of the vagina in pregnancy (Hurley *et al.* 1974). There could, therefore, be an association between reducing vaginal acidity, changing bacterial flora and preterm labour.

Minkoff *et al.* (1987) attempted to define a vaginal pH value above which preterm labour was more likely and found that the risks increased when pH was greater than 4·4. The upper limit of vaginal pH is widely accepted as 4·5 (Paavonen 1983). The range of vaginal pH during normal pregnancy has not been well defined; litmus paper has usually been used to assess it and studies have been cross-sectional. A microelectrode as used in this study allows precise and consistent siting of the electrode and an accurate digital read-out of the pH. This longitudinal study shows that the vaginal pH is relatively constant throughout pregnancy. Only two women in the longitudinal study went into preterm labour but both had a mean pH >5. The vaginal pH during early labour in those women delivered preterm was significantly higher than in those delivered at term.

Bacterial infection is associated with a less acid pH (Peeters *et al.* 1972). It is not clear whether the increased pH encourages bacterial growth or whether bacterial growth alters the local pH. Women with bacterial infections were therefore excluded from the determination of the normal range.

The results of this study show that *C. albicans* and lactobacilli can change the pH of the surrounding environment *in vitro*, and that they maintained a final pH at about 4 despite their increased growth. This is in keeping with the fact that lactobacilli are an important factor in maintaining vaginal acidity and also that *C. albicans* are able to flourish at the normal range of vaginal pH.

With *E. coli*, growth increased with rising pH and the pH tended to fall only slightly as the bacteria proliferated during the incubation period. This supports the proposition that a pathogen such as *E.coli* might be expected to flourish in a vaginal environment with a pH higher than the normal. Such results, however, must be interpreted with caution as they may not be applicable *in vivo*.

Pathogens such as *E. coli* have been shown to release phospholipase A_2 and thereby increase arachidonic acid metabolism in the amnion in favour of the production of PGE_2 which may trigger labour (Bennett *et al.* 1987). It could be that overgrowth of pathogens is due to an increased vaginal pH rather than the reverse. This in turn may be due to decreased concentration of lactobacilli or to some other biochemical alteration in the vaginal environment. These preliminary findings may have implications in screening for, and possibly treating, preterm labour. A large longitudinal study of vaginal pH throughout pregnancy would be worthwhile. Also studies of the effect of pH on bacterial enzymes such as phospholipase and collagenase which might initiate preterm labour or rupture of the membrane would seem to be indicated.

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Maternal and paternal alcohol consumption and miscarriage

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Summary. To explore the role of parental alcohol consumption in miscarriage we interviewed 80 women who miscarried about their own and their partners' drinking habits. A control group of 81 gestational-age-matched women whose pregnancy ended in the delivery of a healthy infant at term were similarly questioned. The use of alcohol by women and men was equally frequent in both groups. Before pregnancy, the mean alcohol consumption per week had been about 1–2 drinks for the women and 4–5 drinks for the men. During the presumed day of conception, 13% of the women who miscarried and 11% of the women in the control group had drunk on average 3–4 drinks; the other women had been abstinent at this time. Of the partners, 13% and 15%, respectively, had taken a mean of 4–5 drinks. In both groups 58% of the subjects continued to consume alcohol during pregnancy. The mean consumption was about one drink a week by the women who miscarried and half a drink a week in the control group. Of women who miscarried, 36 had a blighted ovum and in this subgroup alcohol consumption in both women and men was similar to that in the other women who miscarried and their partners, suggesting that alcohol is not causally related to the development of a blighted ovum. These results suggest that moderate maternal or paternal alcohol consumption does not increase the risk of miscarriage.

Drinking during pregnancy has been connected with an increased risk of miscarriage in the second trimester, but the association was found only when maternal alcohol consumption exceeded 4–7 drinks per week (Harlap & Shiono 1980; Kline *et al.* 1980; Sokol *et al.* 1980). Whether the possible effect of alcoholism on miscarriage is a result of the direct toxic effect of ethanol on the ovum, placenta, or uterus, or on all of these together, is unknown. Furthermore, a drinking woman often marries a drinking man, but the role of paternal drinking in miscarriage has not been addressed. Such an association is supported by data on poor sperm quality in alcoholic men (Van Thiel *et al.* 1974; Välimäki & Ylikahri 1983), and in animal experiments by ethanol-induced chromosomal abnormalities (Brown *et al.* 1979; Kaufman 1983). We there-

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fore arranged a study of the role of maternal and paternal alcohol use in miscarriage.

Subjects and methods

Eighty women experiencing a threatened miscarriage between 6 and 23 weeks gestation (mean 10·7, SD 4·5 weeks) were included in the study (Table 1). They were otherwise healthy except for one who had diabetes controlled with insulin. The women were admitted to hospital, but in spite of bed-rest the pregnancy ended in miscarriage. All women underwent curettage of the uterus, and the tissue obtained was studied by microscopy. Based on histological findings in all 80 women and ultrasonography in 49 before the miscarriage, 36 (45%) proved to have a blighted ovum, whereas in 44 (55%) the presence of a fetus could be shown. A control group comprising 81 women matched for gestation who had no sign of threatened miscarriage were studied (Table 1). These women were selected from a routine ultrasound screening in our hospital and they were delivered of healthy infants at term. Smoking was equally common in both groups (Table 1), and no marked differences in social class distribution could be seen between the two groups.

A nurse specially trained for alcohol studies interviewed all the women about their use of alcohol and cigarettes. Alcohol consumption before pregnancy, during the presumed day of conception, and during pregnancy was assessed separately. The nurse also recorded data on paternal alcohol consumption, such as the age at initial use and frequency of drinking, the amount of alcohol consumed on each occasion, and possible social consequences of alcohol abuse. In addition, the use of drugs or stimulants other than alcohol was recorded.

The women who miscarried were interviewed after the miscarriage before they left hospital. The control women were interviewed immediately after the ultrasound examination

The significances of the differences between the groups were tested by Student's *t*-test completed with the correction of Bonferroni.

Results

Fifteen of the women who miscarried (19%) and 16 in the control group (20%) did not drink alcohol before or during pregnancy. Before pregnancy, the mean alcohol consumption of drinking women had been approximately 1–2 drinks a week in both groups (1 drink = 13 g of ethanol). Alcohol consumption of the drinking husbands had been about 4–5 drinks a week, and was similar in both groups (Table 2).

Ten of the women who miscarried (13%) and nine control subjects (11%) had drunk a mean of 3–4 drinks on the presumed day of conception (Table 2). Ten partners of women who miscarried and 12 men in the control group had taken a mean of 4–5 drinks of alcohol on the presumed day of conception (Table 2).

After recognition of pregnancy, 84% of the women who miscarried and 81% of the control women had decreased their alcohol consumption, and 42% of the women in each of the two groups were abstinent thereafter. The mean alcohol consumption of those who continued

Table 1. Clinical characteristics of the subjects in the study

	Miscarriage group (*n*=80)	Control group (*n*=81)
Maternal age (years)		
mean (SD)	30·9 (6·3)*	27·5 (7·2)
(range)	(21–41)	20–38)
Gestational age (weeks)		
mean (SD)	10·7 (4·5)	13·4 (6·1)
(range)	(6–23)	(7–24)
Smoking women	21	20
Nulliparous women	36	21
Number with previous miscarriage	25	16
Paternal age (years)		
Mean (SD)	35·0 (5·3)	30·4 (6·3)
(range)	(20–44)	(21–48)
Smoking men	28	30

*$P<0.05$ when compared with control women.

Table 2. Alcohol consumption of patients and control subjects (abstinent subjects excluded)

Alcohol consumption	Miscarriage group (*n*=80)	Control group (*n*=81)
Before pregnancy		
Number of women	65 (81%)	65 (80%)
Alcohol (g/week)		
mean (SD)	25 (32)	21 (56)
(range)	(3–120)	(3–450)
Number of men	68 (85%)	72 (89%)
Alcohol (g/week)		
mean (SD)	52 (82)	54 (85)
(range)	(3–450)	(3–450)
On the presumed date of conception		
Number of women	10 (13%)	9 (11%)
Alcohol (g)		
mean (SD)	44 (35)	48 (45)
(range)	(15–120)	(30–160)
Number of men	10 (13%)	12 (15%)
Alcohol (g)		
mean (SD)	59 (74)	56 (42)
(range)	(30–225)	(15–160)
During early pregnancy		
Number of women	46 (58%)	47 (58%)
Alcohol (g/week)		
mean (SD)	16 (27)	8 (14)
(range)	(3–120)	(3–23)

drinking during pregnancy was only ½–1 drink a week (Table 2).

The use of alcohol by the women who miscarried was analysed separately with respect to the presence of a fetus or a blighted ovum, but there were no differences between these two subgroups in maternal or paternal drinking habits before pregnancy, during the day of conception, or during pregnancy.

Discussion

Information about their own and their partner's use of alcohol was obtained by interview from 161 pregnant women. This method, in common with all methods employed for the assessment of alcohol use, is open to criticism, and the general consensus is that the reported consumption is less than the actual, no matter what method has been employed (Chick *et al.* 1981; Skinner *et al.* 1981; Alanko 1984). However, interview is still the most widely used method, and is superior to the best laboratory markers of alcohol abuse (Skinner *et al.* 1981, 1986). We did not attempt to interview the partners of the women personally, since it soon became apparent that the women could reveal the alcohol consumption of their partners in our study as in some previous studies (McAuley *et al.* 1978; Karhunen *et al.* 1986).

Consumption of at least 1–2 drinks a day (Harlap & Shiono 1980), or as little as two drinks twice a week (Kline *et al.* 1980) has doubled the risk of a second-trimester miscarriage. In the present study, only 58% of the women in both groups drank alcohol during pregnancy. Also the amounts of alcohol consumed were quite small, corresponding to approximately one drink per week for those who miscarried and half a drink per week for the control group of women. This volume of drinking accords well with the data in our prospective work showing that 90% of pregnant women take 0–2 drinks a week (Halmesmäki *et al.* 1987). Our present data are also in harmony with several studies which have failed to show any association between maternal drinking involving two or fewer drinks a week and fetal damage (Tennes & Blackard 1980; Rosett *et al.* 1983; Wright *et al.* 1983; Halmesmäki *et al.* 1987). However, we must remember that it may be difficult to separate the effect of alcohol use from the effects of smoking and social deprivation which are often associated with heavy drinking, and which may increase the risk of miscarriage. Furthermore, the number of subjects was small in our study, and the possible association between alcohol use and miscarriage could perhaps emerge in a larger study.

Approximately 60% of miscarriages are associated with chromosomal defects in the ova (Knowles 1987). They are probably consequences of natural occurrences, and the combination of maternal and paternal genes does not always result in a viable ovum. In this regard, paternal factors, such as alcohol abuse, may gain significance, particularly because ethanol induces chromosomal aberrations in animals (Brown *et al.* 1979; Kaufman 1983). Clinically these pregnancy losses may present as early 'subclinical' miscarriage or blighted ovum. We therefore compared the use of alcohol between miscarriages with a fetus and those with a blighted ovum, but we found no differences in the habits of alcohol consumption between these subgroups. Moderate alcohol use thus may not be connected with the development of a blighted ovum.

We conclude that there is no difference in the maternal and paternal use of alcohol between pregnancies that end in miscarriage and those that continue to term. Two or fewer alcoholic drinks a week for women and four or fewer drinks a week for men seem not to be a risk factor for miscarriage.

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Atopy in couples with unexplained infertility

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Summary. In an initial exploratory study, proneness to atopy was measured by specific allergen history, allergen skin testing and plasma IgE in couples with unexplained infertility and in a comparison group of couples who had recently had a child. At least one of the assessments was positive in 29 out of 47 infertile couples and in 52 out of 103 controls, but only five of the infertile group and two of the fertile group had all three assessments positive. Raised IgE levels occurred significantly more often in the infertile couples than in the comparison group.

Abnormal allergic response to everyday substances as well as to unaccustomed stimuli (atopy) has been linked to many disease processes. The key to the reaction is the mast cell system. These cells are present in the connective tissue throughout the body including the reproductive organs such as testis (Maseki *et al.* 1981) and uterus (Sheppard 1980). If stimulated, mast cells may give rise to an immediate IgE-dependent hypersensitivity reaction; a variety of local reactive substances (Lubs 1983) stored in the granules are released (Caulfield *et al.* 1980), and a chain reaction results which can lead to tissue destruction (Kaliner 1979). If this occurs in key reproductive organs their delicately balanced functions could be deranged and cause infertility.

To substantiate such a hypothesis is difficult. Infertility involves many confounding variables and a definitive diagnosis of atopy includes the detection of mastocytosis which necessitates tissue biopsy. However, a comprehensive specific allergenic history, allergen skin tests and IgE measurements have been found helpful in identifying those at risk of allergic disease (Cohen 1985), and using couples where no cause for childlessness can be found confers as much homogeneity as is possible. Therefore, in this study, these three assessments were used to establish the atopic characteristics of a group of couples with unexplained infertility and to compare them with couples who had recently had a child.

Subjects and methods

All patients selected for the study attended the Rotunda Hospital, Dublin, during 1985. The study included 47 infertile couples and 103 women who had given birth and their partners. All gave signed informed consent.

Infertile couples were classified as having unexplained infertility on the basis of an absolutely normal fertility profile (Harrison *et al.* 1980). This included a search for sperm antibodies using the mixed antiglobulin reaction (MAR test) IgG and IgA on semen, the sperm–cervical mucus contact test and the gelatin agglutination tests on male and female serum (WHO 1987).

Distribution of social class was similar for the two groups. Mean age of the infertile females was 31·4 (range 23–47) years and the fertile females 32·1 (19–42) years. Mean age of the infertile males was 30·2 (20–45) years and the

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fertile males 32 (19–47) years. Average length of infertility was 7·2 years (18 months–13 years).

Atopy measurements

A full history for allergic disease was obtained using a case history chart for allergic diseases published by Bencard UK. House dust mite, house dust, feathers, cat fur, dog hair and B2 grasses allergens (skin test, Bencard Allergens and Skin Test Reaction Chart) and their controls were tested on each subject's forearm using the skin prick method. A positive reaction as read 'blind' by a third party was considered present when a significant wheal or flare was noted.

Total serum IgE was estimated using the paper radioimmunosorbent test (PRIST, Pharmacia Diagnostics UK). This uses anti-IgE covalently coupled to a paper disc which is first incubated with IgE present in the patient's serum sample. Antibodies against IgE are then added and measurements taken by a gamma counter. Reference levels estimated for the method give a geometric mean of 14 i.u./ml (SD 41, 2 SD 122). Atopic genesis is considered highly probable when the IgE level exceeds 100 i.u./ml.

Statistical analysis

An 'exploratory' analysis was performed using χ^2 on all six basic comparisons. Multivariate analysis (discriminant analysis) was then used to discover whether variables in combination gave information as to whether a couple were more likely to be infertile.

Results

In the infertile group (Table 1) at least one positive variable was found in 29 of 47 couples (17 male and 15 female). One or other of the partners had a significant history in 10, positive skin test reactions in 14, and IgE >100 i.u./ml in 20 In only five (four male and one female) were all three measurements positive.

In the 103 controls (Table 2) at least one positive was found in 52 couples (32 male and 29 female). In 13 couples one partner had a positive history, in 32 at least one partner had a positive skin test reaction. In 24 at least one partner had an IgE level >100 i.u./ml. However, in only two women were all three variables positive and there were no males with all positive.

Exploratory analysis showed significant differences between the group with unexplained infertility and the controls in the male history ($P<0{\cdot}01$) and in male IgE ($P<0{\cdot}05$). Multivariate analysis showed that the best discrimination between the two groups was to record couples as positive if one or both of them was IgE positive. This gave 20 positives amongst the unexplained infertile couples and 24 positives in the controls ($P<0{\cdot}02$ with χ^2-tests of these figures). Were these criteria used as a diagnostic test it would have a specificity of 77% and a sensitivity of 43% on our data.

Discussion

It is evident from our knowledge of other disease processes involving mast cells that it is tenable that excessive activity may occur in reproductive cells and thus be associated with infertility as primary cause or secondary effect. Mast cell secretory granules contain many active prin-

Table 1. Presence of abnormal allergic factors in 47 couples with unexplained infertility

Variable	Positive subjects (couple number)
History of allergy	
Male	7*, 12, 17, 22*, 28, 39*, 40*
Female	22, 35, 36, 39, 41*
Allergen skin tests	
Male	7*, 9, 22*, 39*, 40*, 42, 44, 46
Female	4, 18, 21, 22, 24, 27, 39, 41*
IgE >100 i.u./ml	
Male	2, 7*, 9, 12, 15, 22*, 30, 31, 37, 39*, 40*, 41, 45
Female	5, 18, 24, 26, 27, 32, 41*, 43, 45

* All three variables positive

Table 2. Presence of abnormal allergic factors in 103 control puerperal females and partners

Variable	Positive subjects (couple number)
History of allergy	
Male	8, 22, 59
Female	1, 4, 16, 46*, 61*, 63, 77, 79, 95, 102
Allergen skin tests	
Male	13, 14, 16, 21, 29, 31, 32, 38, 42, 46, 48, 49, 59, 60, 62, 73, 74, 85, 89, 93, 94
Female	3, 5, 9, 16, 19, 21, 28, 32, 37, 40, 46*, 49, 61*, 88, 95, 96
IgE >100 i.u./ml	
Male	9, 14, 15, 54, 62, 72, 74, 75, 76, 77, 85, 89, 90, 96
Female	5, 14, 17, 46*, 55, 61*, 66, 68, 69, 70, 88, 89

* All three variables positive.

ciples including hyaluronidase and protease enzymes which are known to affect the functional activity of cells (Maseki *et al.* 1981). The trigger to such excessive mast cell activity in infertile couples is, however, more difficult to perceive. The obvious candidate, seminal plasma, has few reports of postcoital hypersensitivity reactions cited in the literature (Shapiro *et al.* 1981), despite the presence of some 30 potential antigens (Jones 1980).

The more accurate atopy diagnostic variables of mast cell counts or mastocytosis are not practical propositions in the general day-to-day clinical situation where an in-depth history, skin reaction tests and raised IgE levels have been found to correlate well with each other and with a high predictive value for atopy. It is not necessary to have positives in all three areas for atopy to be suspected (Stafford 1987), nor is it necessary for positives to be present in both male and female. A relatively minor problem such as atopy in one partner could be of aetiological importance even if the other partner were absolutely normal.

In this study, we used the presence of a single positive variable to suggest an abnormal allergic response, and only the history and IgE levels in males were significantly different between the two groups. When the three variables were considered in combination, only raised IgE levels occurred significantly more often in the infertile group and could be a possible discriminant that could identify a tendency to atopy.

It is possible that more rewarding results might have been obtained by looking at couples where a specifically identified 'cause' for their infertility might have an atopic basis, e.g. 'sperm antibodies' (Jones 1980), for although the use of couples with unexplained infertility by definition confers a degree of uniformity of the subjects under scrutiny by eliminating many possible interactive factors, atopy may not be one of the hidden causes that remain. However, in the infertile couple, whatever the aetiology, on the basis of this initial exploratory study, unless more specific methodology is developed to complement the initial IgE screen, any possible links between atopy and the aetiology of their childlessness must continue to remain conjecture.

Acknowledgments

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Suppression of gonadotrophin secretion does not reverse premature ovarian failure

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Summary. The effect of prolonged inhibition of gonadotrophin secretion was studied in 12 women with premature ovarian failure. All the patients had plasma concentrations of follicle-stimulating hormone (FSH) >20 i.u./l, and in six, primordial follicles had been seen on ovarian biopsy. Goserelin (Zoladex, ICI), a depot synthetic analogue of luteinizing hormone-releasing hormone (LHRH) was administered by three consecutive 4-weekly injections. Plasma concentrations of luteinizing hormone (LH) fell from 34 (SD 11) i.u./l to 2·4 (SD 1·9) i.u./l, and plasma concentrations of FSH fell from 106 (SD 29) i.u./l to 4·5 (SD 2·6) i.u./l 4 weeks after the first injection. Plasma concentrations of gonadotrophins returned to pretreatment values in every patient within 9 weeks of the final injection of goserelin. Regular ultrasonography during the period following the final injection failed to demonstrate the development of ovarian follicles in any patient, and plasma concentrations of oestradiol remained below 100 pmol/l. This study has failed to show that suppression of gonadotrophin secretion reverses premature ovarian failure.

Premature ovarian failure is defined as amenorrhoea associated with postmenopausal plasma gonadotrophin concentrations occurring before the age of 40 (Rebar *et al.* 1982). Histological examination has revealed that in the larger proportion of these women the ovaries are depleted of follicles and consist mainly of fibrous stroma However, approximately 30% of these women display numerous primordial follicles which are apparently resistant to gonadotrophin stimulation (Russell *et al.* 1982; Friedman *et al.* 1983). The cause of both premature follicular depletion and gonadotrophin resistance remains unclear, although various immunological, infectious and iatrogenic factors have been identified There are reports of spontaneous resumption of menstruation and pregnancy after documented premature ovarian failure (Shangold *et al.* 1977; Szlachter *et al.* 1979).

Some reports show ovulation to have resumed after treatment with both exogenous oestrogens (Petsos *et al.* 1986) and LHRH analogues (Menon *et al* 1983). This was thought to have been a result of suppression of gonadotrophin secretion and led to the hypothesis that premature ovarian failure was a self-perpetuating defect (Petsos *et al.* 1986). It was argued that, even if the ovarian failure was temporary, any

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developing antral follicle would become atretic as a consequence of the high plasma FSH concentration before secreting enough oestradiol to inhibit the gonadotrophs.

Suppression of gonadotrophin secretion broke this self-perpetuating cycle and this explained resumption of ovulation after treatment with oestrogens and LHRH analogues.

We were interested to test this hypothesis by suppression of gonadotrophin secretion for 3 months in 12 women with established premature ovarian failure with goserelin (Zoladex, ICI, Macclesfield, UK) a depot luteinizing hormone-releasing hormone agonist.

Subjects and methods

Twelve women were recruited to the study. Their ages ranged from 26 to 41 years and all had secondary amenorrhoea of 2–12 years' duration. Premature ovarian failure was diagnosed by a plasma FSH concentration of >20 i.u./l and a plasma oestradiol concentration <100 pmol/l on at least two occasions. In 11 women the aetiology was unknown and in one it was a result of chemotherapy for Hodgkin's disease. In six women laparoscopic ovarian biopsy had demonstrated the presence of primordial follicles. No patient had been prescribed oestrogen or progestogen therapy within 3 months of the study. The protocol was approved by the ethics committee.

Goserelin, 3·6 mg, was administered by 4-weekly subcutaneous injection. We have already demonstrated that this drug successfully and reversibly suppresses gonadotrophin secretion (Thomas *et al.* 1986*a*). Blood was sampled for estimation of plasma LH, FSH and oestradiol immediately before each injection. A regimen of regular surveillance of ovarian function was begun 28 days after the final injection of goserelin. This consisted of ovarian ultrasonography every 3 days combined with synchronous blood sampling for estimations of gonadotrophin and oestradiol concentrations, and daily saliva collection for estimation of progesterone concentration. The techniques of ultrasonography and gonadotrophin and steroid radioimmunoassays have been described previously (Thomas *et al.* 1986*b*). It was intended to perform daily ultrasonography once follicular development was observed. In the event of no follicular development, this surveillance was continued until 10 weeks had elapsed since the final injection.

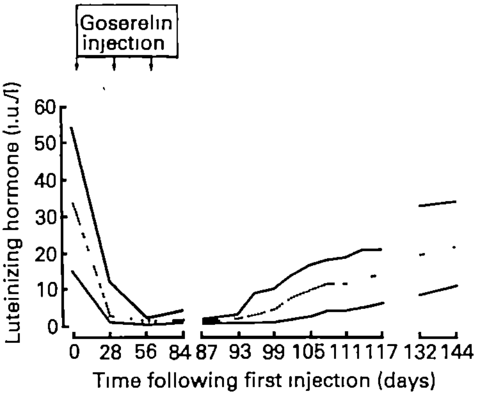

Fig. 1. Range and mean of plasma luteinizing hormone concentrations before, during, and after three 4-weekly injections of goserelin. (Note alterations in time-scale.)

Results

All the patients completed the study and no difficulties were encountered with either the injections of goserelin or clinically significant side-effects. Regular measurement of routine haematological and biochemical indices did not show any alterations from normal baseline values.

Figures 1 and 2 show that the plasma concentrations of LH and FSH fell within 28 days of the first injection of goserelin to normal follicular phase values. This suppression was maintained throughout the treatment period. Following the end of the therapeutic effect of goserelin the plasma concentrations of both LH and FSH returned to within the pretreatment range in all patients within 10 weeks of the final injection. Plasma concentrations of oestradiol before treatment were below 100 pmol/l in all patients. These concentrations did not rise during or after treatment in any patient. In addition, regular pelvic ultrasonography, performed at least every 3 days whilst the plasma gonadotrophin concentrations were rising, failed to demonstrate any evidence of follicular growth.

Discussion

This study has shown that goserelin will suppress gonadotrophin secretion in patients with premature ovarian failure. The suppression was consis-

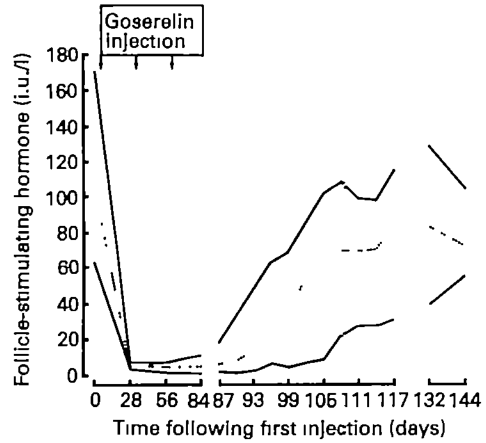

Fig. 2. Range and mean of plasma follicle-stimulating hormone concentrations before, during, and after three 4-monthly injections of goserelin. (Note alterations in time-scale.)

tent throughout the treatment period and no patient suffered any major side-effects. However, the return of gonadotrophin secretion did not stimulate follicular growth, and plasma FSH concentration returned to pretreatment levels in all women within 8 weeks of the final injection. Menon *et al.* (1983) considered that pituitary desensitization may have been more successful in their four patients if the treatment period had been extended beyond 20–24 days. We have not been able to demonstrate that increasing this period to 3 months gave any therapeutic benefit.

The inability of pituitary desensitization to reverse premature ovarian failure means that the ovarian defect is not perpetuated by elevated plasma gonadotrophin concentrations. This leaves unanswered the question as to why other studies have reported occasional spontaneous resumption of ovarian function in some patients. In some reports the diagnostic criteria for premature ovarian failure are not as precise as in this study (Rebar *et al.* 1982; O'Herlihy *et al.* 1980). It could be that ovarian function returned in those patients who were oligo-ovulatory but could not be strictly considered to have premature failure. However, criteria were stricter in other studies (Menon *et al.* 1984; Tan *et al.* 1986) and yet ovarian function resumed in some women. It may be that there is a defect in the FSH receptors on the granulosa cells (Russell *et al.* 1982) and that this does reverse spontaneously in some women. Our study does not indicate that this defect is perpetuated by raised plasma gonadotrophin concentrations.

The implications of these results are twofold. Firstly, it appears that gonadotrophin suppression should not be recommended as therapy for women with premature ovarian failure. If they desire fertility then in-vitro fertilization using a donor oocyte should be the initial treatment. Otherwise hormone replacement therapy should be instituted and occasionally stopped to see if spontaneous recovery of ovarian function has occurred (Tan *et al.* 1986). The second implication is the relevance of laparoscopic ovarian biopsy in the management of patients with this problem. The procedure is only justifiable if the information obtained will alter the management. The value of ovarian biopsy has been questioned in the past, especially as regards its technical difficulty (Sutton 1974). There are also reports of successful ovulation after ovarian biopsy has demonstrated no primordial follicles (O'Herlihy *et al.* 1980), presumably because the specimen did not represent the histological structure of the whole ovary. As this study has not been able to demonstrate that the confirmed presence of primordial follicles alters the outcome therapeutically then the information is not discriminating and imparts no prognostic significance. As such, it seems inappropriate to subject patients to laparoscopic ovarian biopsy.

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Long-term follow-up of patients with uterine fibroids after treatment with the LHRH agonist buserelin

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Summary. Ten patients with uterine fibroids palpable abdominally were treated with the luteinizing hormone-releasing hormone (LHRH) agonist buserelin, administered intransally, 300 μg three times daily, for 6 months, and were then followed for a further 12 months. Oestrogen levels were markedly reduced in all patients during treatment. At the end of treatment the mean volume reductions were 44·4% (SEM 3·5) for total uterine volume and 57·3% (SEM 7·4) for volume of discrete fibroids as assessed ultrasonically. There was also marked improvement in associated symptoms. After buserelin therapy was stopped, the total uterine and discrete fibroid volumes returned to, or slightly exceeded, pretreatment volumes within 6 months in five patients, and by 12 months in two patients. Three other patients who underwent surgery for their fibroids during the first 4 months after treatment showed regrowth of fibroids to pretreatment size. Four comparable asymptomtic untreated patients showed no significant change in the total uterine or fibroid volume during six monthly ultrasonic assessments. Buserelin therapy may facilitate rather than replace surgery in the management of uterine fibroids.

Uterine fibroids are the most common benign tumours found in women. Until now treatment of symptomatic patients has been primarily surgical, and attempts at medical treatment with progesterone (Segaloff *et al.*. 1949), danazol (Maheux *et al.* 1983) and gestrinone (Coutinho *et al.* 1986) have been disappointing. Clinicians have long recognized that fibroids are dependent on oestrogen for maintaining their growth and size as these tumours are rarely found before puberty, they increase in size during pregnancy or after oestrogen administration and regress after a natural or induced menopause Histological evidence that endometrial hyperplasia may be found in proximity to submucous fibroids suggests that local oestrogen levels may be high (Deligdish & Loewenthal 1970). Further experimental evidence of oestrogen dependency is provided by studies showing increased cytoplasmic oestrogen receptor content in leiomyomatous tissue compared with adjacent normal myometrium (Soules & McCarty 1982; Wilson *et al.* 1980; Tamaya *et al.* 1985). If a state of reduced oestrogen secretion could be induced, this could result in the reduction in growth of fibroids and even their regression.

The continued administration of luteinizing hormone-releasing hormone (LHRH) agonist analogues can effectively reduce circulating oestrogen levels by suppressing the pituitary–

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ovarian function. Several studies have shown the effectiveness of LHRH agonists in the treatment of conditions believed to be dependent on ovarian steroid production, such as endometriosis (Matta & Shaw 1987), precocious puberty (Comite *et al.* 1984), ovarian hyperandrogenism (Chang *et al.* 1983) and menorrhagia (Shaw & Fraser 1984). Recent reports on the use of these agents in patients with uterine fibroids have been encouraging (Maheux *et al.* 1987; Healy *et al.* 1986; Coddington *et al.* 1986; Rolland *et al.* 1986), but they lacked comparisons with controls and long-term measurements of fibroid volumes after discontinuation of therapy. We assessed the effects of the LHRH agonist buserelin [D-Ser-(TBU)^6-des Gly-NH$_2^{10}$ LHRH ethylamide] (Hoechst Pharmaceuticals), administered intranasally to women with large uterine fibroids for 6 months, and who were then followed up for a period of 12 months after treatment.

Patients and methods

Ten women aged 28 to 45 years who all had uterine fibroids that were palpable abdominally were recruited to the study and gave their informed consent. Five of the women were white European, three Negroid, and two Asian. Seven patients presented with menorrhagia, eight had dysmenorrhoea with or without pelvic pain and two were infertile. Seven were nulliparous and two had undergone myomectomy some years previously. None had been treated with sex steroid hormones during the 12 months before or during the 18 months of the study.

Before the treatment each patient was examined under anaesthesia and had a diagnostic curettage to exclude other pelvic pathology. Pretreatment clinical assessments were made by at least two clinicians and the uterine sizes were similar to pregnancies of 12 to 18 weeks. Ultrasound scans showed that two patients had solitary and the remainder multiple fibroids. Each patient received intranasal buserelin, 300 μg, 8-hourly for 6 months beginning on day 2–4 of the menstrual cycle that followed diagnostic curettage. Patients were then followed up for 12 months after treatment was stopped.

Assessments by clinical examination, ultrasound measurements, full haematological and biochemical screening were made bimonthly during treatment and the first 6 months of follow-up, and at 9 and 12 months follow-up. Measurements of serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), and oestradiol-17 β (E2) used the radioimmunoassays described previously (Shaw & Matta 1986) and were made monthly during treatment, and at 2, 4, 6, 9 and 12 months after treatment. Menstrual records and symptom charts were kept by the patients throughout. Total uterine volume and the volume of any identifiable discrete fibroid were measured by one observer (M.N.) who reviewed all serial ultrasound measurements of the three largest dimensions or diameters (length, width and antero-posterior) for each, and calculated the volumes according to the formula used for the volume of an ellipsoid

$$V=\frac{\pi\, abc}{6}$$

—where $\pi=3{\cdot}14$ and abc are the three diameters (Shawker 1980). These measurements were taken by a linear array sector scanner (DIASONICS DRF 100) with a 3·5-MHz transducer. During the follow-up period ultrasound measurements were made during the early follicular phase of the menstrual cycle to allow more reliable comparisons with those obtained during treatment, as we have noted that these measurements vary slightly during different times of the cycle.

Four Caucasian nulliparous women, aged 35 to 44 years, with asymptomatic uterine fibroids that were palpable abdominally, and who opted to receive no treatment, formed a comparison group. The same serial uterine volume and endocrine assessments were made, but at monthly intervals, during the early follicular phase, for 6 consecutive months.

Results

All 10 patients completed 6 months of treatment with buserelin. Marked reduction in plasma oestrogen was achieved in all patients within 4 weeks and was sustained throughout treatment, at or below levels consistent with early follicular phase values. The mean (SEM) E2 values immediately before, during and throughout the follow-up period are shown in Fig. 1.

Apart from an initial light withdrawal bleed at some stage during the first 3 weeks, there were no further true menstrual periods in any patients during treatment. However, irregular, infrequent, light episodes of bleeding without the

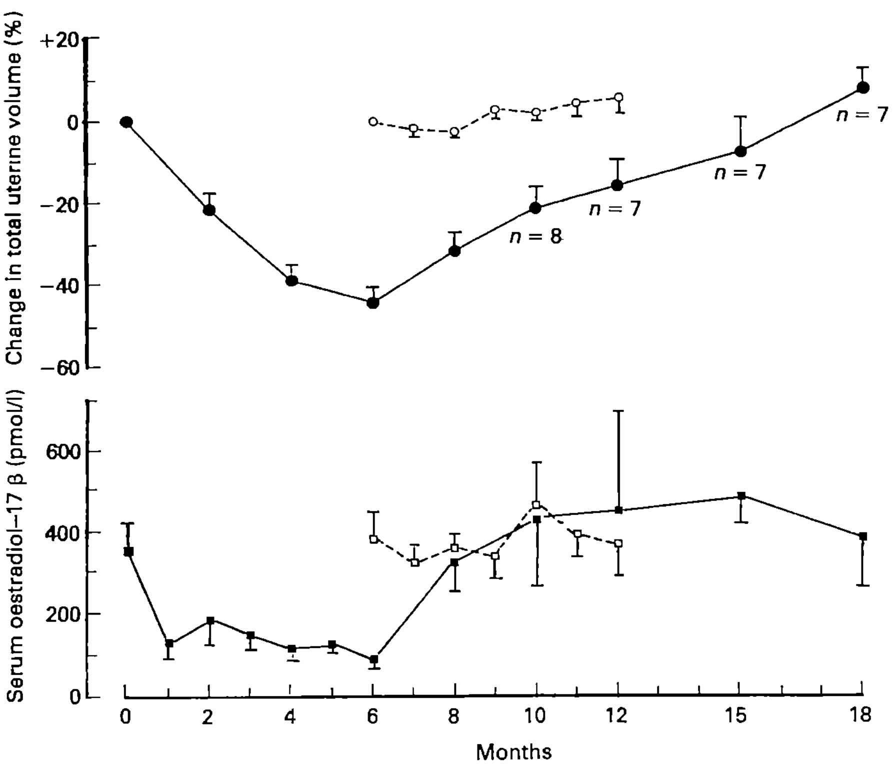

Fig. 1. Mean ±SEM changes in total uterine volume (%) and in serum oestradiol-17β (pmol/l) levels during and after treatment with intranasal buserelin, 300 μg three times daily, in 10 patients with uterine fibroids, and in four control subjects observed without treatment for 6 consecutive months. ●——●, ■——■, Treated (n=10); ○---○, □---□, control (n=4)

usual menstrual symptoms were reported by five patients, and these continued throughout treatment in two patients. All patients reported a remarkable or complete improvement in menorrhagia, dysmenorrhoea, pelvic pain and pelvic pressure symptoms. Treatment was well tolerated by most patients, with hot flushes, the commonest side-effect, being experienced by seven patients. Two of these patients found the hot flushes, accompanied by increased night sweating disturbing their sleep, to be moderately inconvenient, but none of the patients withdrew from the study because of side-effects. Slight reduction in vaginal secretions towards the end of the treatment period was reported by two patients and occasional headaches occurred in three. There were no significant changes in weight, blood pressure, urinalysis, serum liver function tests, urea or electrolytes. Five patients who had haemoglobin values below 11 g/dl (mean 10·3 g/dl) before treatment, due to their menorrhagia, had returned to more normal values (mean 12·4 g/dl) by the end of treatment, without any iron intake. The remaining five patients had mean haemoglobin values of 13·4 g/dl and 14·2 g/dl, before and at the end of treatment respectively.

The mean pretreatment total uterine volume in the 10 patients was 620·8 cm^3 (SEM 85·74, range 330–1032 cm^3) measured by ultrasound. Although there was a wide variation in patients' responses to the low circulating oestrogen levels there was generally a more rapid rate of reduction in these volumes during the first 4 months than the latter 2 months on treatment (Fig. 2). Similarly the clinical uterine size, as assessed by the same clinician, showed a dramatic and comparable rate of reduction, from a mean of 14·7 weeks pregnancy size before treatment to a mean of 10·6 weeks size. The mean volume for the nine identifiable individual discrete fibroids was 87 cm^3 (SEM 29, range 27–155 cm^3). There were seven other individual fibroids which were measured at the beginning of the study but which could not be measured later during treatment because their outline definition was lost due to

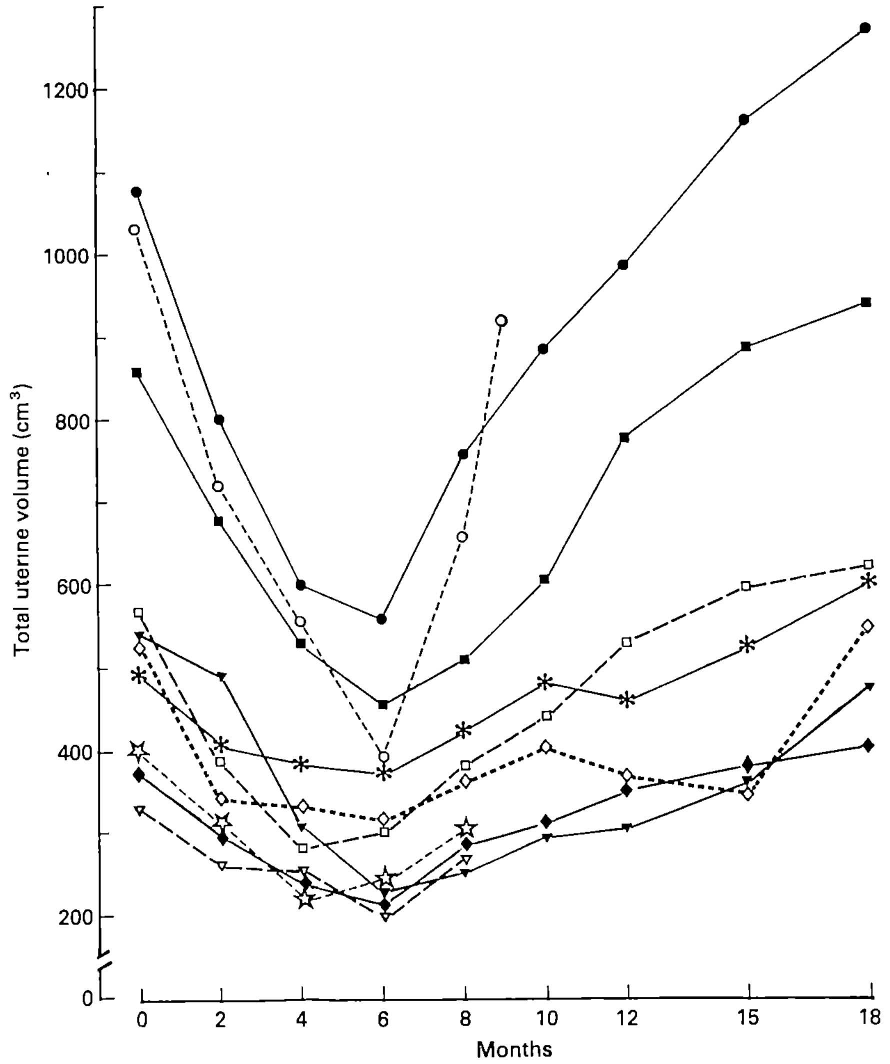

Fig. 2. Total uterine volume (cm³) changes in 10 patients with uterine fibroids, during and after treatment with intranasal buserelin

degeneration or marked shrinkage, and these were excluded from analysis.

Those patients who had the largest pretreatment uterine volumes showed the most striking reductions in size during treatment and the greatest rate of regrowth after treatment (Fig. 2).

Post-treatment follow-up

Regular menstrual cycles resumed in all 10 patients within 32 to 54 days (mean 41 days) after cessation of treatment. Hot flushes ceased within a mean of 31 days, and other side-effects within the first 2 weeks after treatment. One patient had a hysterectomy 3 months after treatment because of prolonged heavy uterine bleeding and associated pain, and two others had a myomectomy 4 months after treatment, one for recurrence of menorrhagia with haemoglobin fall, and the other for infertility surgery and rapidly regrowing fibroids.

In five of the remaining seven patients, the uterine volume had returned to or slightly exceeded the pretreatment value at the 6 months follow-up (Fig. 2), and their symptoms had gradually increased to become as severe as before treatment. In two other patients the uterine volume increased more slowly, but had returned to the pretreatment volume by the 12 months follow-up (Fig. 2).

Discussion

In the present study daily intranasal buserelin therapy for 6 months induced a sustained and reversible hypo-oestrogenic state, a marked reduction in size of fibroids, and relief of the associated symptoms. The reductions in both the total uterine and individual fibroid volumes in our group of women were comparable to those reported in other studies using daily subcutaneous buserelin injections (Maheux *et al.* 1985; Rolland *et al.* 1986), subcutaneous continuous infusion of buserelin (Healy *et al.* 1986), and daily subcutaneous injections of other LHRH agonists (Coddington *et al.* 1986). Because it is easy to use, the intranasal route is preferred, until monthly or longer depot preparations become more widely available. Maheux *et al.* (1987) reported a greater and consistent reduction in fibroid volumes, with fewer side-effects, in nine women who received buserelin intranasally, when compared with another group of 12 women receiving buserelin subcutaneously, even when the latter group achieved greater reductions in serum oestradiol levels.

In the present study, treatment was well tolerated, and often accompanied by an increased sense of well-being. The induced amenorrhoea or reduced uterine blood loss resulted in increased haemoglobin concentrations, correcting anaemia in some patients without the need for iron supplementation. The major side-effect of treatment was recurrent hot flushes, sometimes accompanied by night sweats. Other symptoms of oestrogen deficiency were relatively uncommon.

There was a wide variation in the individual sensitivity of the fibroid tumours to the induced reduction in plasma oestrogen levels, with an overall reduction in uterine volume of between 23% and 62% of the pretreatment volumes, by the end of 6 months treatment. This variation in response may well be explained by additional factors which influence fibroid tumour growth such as growth hormone (Spellacy *et al.* 1972) and racial, genetic and metabolic factors. Our observation that women with the largest uterine fibroids had the greatest reductions in volume would confirm similar findings by others (Coddington *et al.* 1986). Differences in the relative proportions of collageneous and muscular tissue and the receptor content of these tumours may in part explain this variation in response.

The rate of reduction in volume associated with LHRH agonist therapy is much greater than that observed in the immediate postmenopausal period, probably because of the relatively swifter reduction in circulating oestrogen levels in the LHRH agonist group. The rate of enlargement after completion of treatment was rapid, and most patients recovered their pretreatment volume by 6 months and all of them by 12 months after treatment. This was much faster than the rate of growth in our untreated control subjects with normal ovarian function, who showed little change in volume over the 6-month review period. The reason for this is not clear, and further studies into the mitotic patterns in both groups may increase our understanding.

This study is the first long-term follow-up of patients treated with LHRH agonists, and our findings question the stated role of this treatment and some assumptions made by previous studies. The return of fibroid volumes in most patients to their pretreatment size within the first 6 months after treatment suggests that the use of these agents will not replace surgery in the long-term management, as has been hoped previously (McLachlan *et al.* 1986; Healy *et al.* 1986). The major indication for using LHRH agonists in this condition would seem to be treatment for 3 to 4 months before myomectomy or hysterectomy as most patients showed the maximum reduction in uterine size during the first 4 months of therapy with a much slower rate of reduction between 4 and 6 months. The reduction in fibroid size before the operation might help to shorten and simplify the operative procedure and reduce postoperative morbidity. Our own studies have shown a significant increase in impedance to blood flow in both the uterine and fibroid vasculature, as measured by Doppler ultrasound, thus signifying reduction in blood flow after a 4-month course with intranasal buserelin (Matta *et al.* 1988*a*). If uterine fibroids are treated surgically immediately after such a course of therapy intra- and postoperative blood loss may be markedly reduced, with consequent reduction in postoperative risks of infection, anaemia and adhesion formation. Prospective randomized studies to investigate this are in progress. Furthermore, Buttram (1986) suggested that the pregnancy rate after myomectomy is inversely related to the size of the fibroid before operation, another reason for attempting to reduce the size of these tumours pre-operatively.

The fibroids enlarged again with the resumption of ovarian oestrogenic secretion after cessation of LHRH agonist therapy; this suggests that the volume reduction was a temporary response to the low levels of oestrogen induced by treatment and may indicate that the leiomyomatous cells or tissue shrank rather than resorbed. Another possible mechanism is that oestrogen deficiency may indirectly cause fibroid tumour shrinkage by reducing the uterine blood flow (Matta *et al.* 1988*a*), and hence the blood volume contained within the fibroids. It has been established in animal studies that oestrogens can cause vasodilatation and increase in the uterine arterial blood flow (Resnick *et al.* 1974).

These agents should not be administered indefinitely because of the potential risk of bone mass loss associated with prolonged oestrogen deficiency. We have demonstrated in a longitudinal study that when buserelin was administered intranasally, 400 μg three times daily, to 13 premenopausal women there was an associated small but significant reduction of 6% in their mean lumbar vertebral trabecular bone density at the end of 6 months treatment; this loss was reversed 6 months after discontinuation of therapy (Matta *et al.* 1987; Matta *et al.* 1988*b*). For the same reason we have reservations about advocating the use of LHRH agonists in perimenopausal symptomatic women (McLachlan *et al.* 1986; Van Leusden 1986; Rolland *et al.* 1986; Friedman *et al.* 1987) with the aim of controlling their symptoms until natural occurrence of the menopause. Accelerated bone loss occurs in oophorectomized premenopausal women and in all postmenopausal women; it is minimized by oestrogen therapy. It seems unwise to impose bone loss as a side-effect of therapy in women who will develop further osteoporosis after the natural menopause.

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Menstrual regulation by intramuscular injections of 16-phenoxy-tetranor PGE_2 methyl sulfonylamide (sulprostone). A multicentre study

WORLD HEALTH ORGANIZATION

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Summary. In a previous study we have shown that three intramuscular injections of 0·5 mg of the prostaglandin analogue, sulprostone (16-phenoxy-W-17,18,19,20-tetranor PGE_2 methyl sulfonylamide), were equally effective as vacuum aspiration for menstrual regulation in women with a delay of up to 21 days in the onset of expected menses. To assess whether lower doses of the prostaglandin could be effective if treatment were restricted to women with a delay of menses of up to 14 days, a multicentre trial investigated the effect of two injections of 0·25 mg sulprostone given with a 4-h interval. After an interim analysis showed a clinically unacceptable low rate of complete abortion (41%) amongst the 64 pregnant women thus treated, the dose was doubled to two injections of 0·5 mg. In the group of 51 pregnant women treated with the increased dose, the frequency of complete abortion (67%) was significantly higher although still well below the 91% success rate achieved in our previous study. Both the duration and the subjective vaginal blood loss were greater in women with complete abortion than in those with incomplete abortion or continuing pregnancy. It is concluded that the sulprostone dose used in our previous study (3×0·5 mg) represents the minimal, required dose for menstrual regulation.

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Menstrual regulation, also known as menstrual extraction, endometrial aspiration and minisuction, is a variant of suction curettage (vacuum aspiration) that is usually limited to the first 2 weeks after a missed menstrual period (Van der Vlugt & Piotrow 1973). In theory, neither anaesthesia nor dilatation is required although local anaesthesia is often used to minimize vasovagal symptoms, and mechanical dilatation of the cervix may be needed in some women. A medical method for menses induction would be an attractive alternative, provided the procedure were safe for both pregnant and non-pregnant women and resulted in a high frequency of complete abortion.

Because of their unique ability to stimulate uterine contractility, even in very early pregnancy, prostaglandins, particularly the newer synthetic prostaglandin E (PGE) analogues that have a more specific effect on the myometrium and can be administered vaginally or intramuscularly, offer the prospect of such a medical alternative. One of these PGE analogues, 16-phenoxy-W-17, 18, 19, 20-tetranor PGE_2 methyl sulfonylamide (sulprostone), was recently compared by us with vacuum aspiration (WHO Task Force on Post-ovulatory Methods for Fertility Regulation 1987). In that study a total of 473 women, including 54 non-pregnant subjects, with a delay of up to 21 days in the expected onset of menses were randomly allocated to treatment with either sulprostone (three intramuscular injections of 0·5 mg at 3-h intervals) or vacuum aspiration. With few exceptions, administration of sulprostone induced vaginal bleeding in both pregnant and non-pregnant women, but the duration and subjectively perceived amount of bleeding were greater than after vacuum aspiration. Both treatments were equally effective in terminating pregnancy with complete abortion rates of 91% and 94% for prostaglandin treatment and vacuum aspiration, respectively However, gastrointestinal side-effects and lower abdominal pain requiring intramuscular analgesia were more common after sulprostone than after vacuum aspiration.

The aim of the present study was to investigate whether a lower dose of the prostaglandin analogue would be equally effective in women with a shorter menstrual delay of up to 14 days.

Patients and methods

Healthy, informed volunteers were recruited for this trial which had been approved by the World Health Organization's Secretariat Committee on Research involving Human Subjects and by the corresponding local committees of the nine participating centres. Except for Tianjin, all these centres had also participated in our previous study (WHO Task Force on Post-ovulatory Methods for Fertility Regulation 1987).

Criteria for admission to the study included at least one previous full-term pregnancy, a delay in the onset of menses of up to 14 days, and a normal general and gynaecological history and examination.

Two dosages of sulprostone were used in the study. Initially, the women received two intramuscular injections of 0·25 mg sulprostone with a 4-h interval (low-dose group) but because an interim analysis indicated a clinically unacceptable high failure rate in the first 79 women (see Results), the dosage was subsequently doubled to two doses of 0·5 mg given at the same 4-h interval (high-dose group; $n = 97$). When this dose also proved to be insufficiently effective, the trial was discontinued for ethical reasons.

All women were admitted to the hospital on the day of prostaglandin treatment for at least 8 h. On admission a urine sample for hCG testing or blood sample for β-hCG assay was obtained for retrospective classification of the subjects as pregnant or non-pregnant. After administration of the prostaglandin analogue, vital signs and body temperature were recorded at regular intervals, and the onset of bleeding, uterine pain and side-effects were noted.

The outcome of treatment was assessed during three follow-up visits at 1, 2 and 6–8 weeks after prostaglandin administration using the same criteria as used in our previous study. Thus, in subjects with a positive blood or urine hCG test before treatment, a first assessment of the outcome of therapy (complete abortion, incomplete abortion or continuing pregnancy) was made at the second follow-up visit. This assessment was based on the duration and amount of bleeding, the level of plasma β-hCG or urinary pregnancy test, gynaecological examination and, if necessary and available, ultrasound examination. Intervention before the second follow-up visit was not allowed unless clinically indicated, e.g. for heavy bleeding. In such cases, the outcome was classified as an incomplete abortion. If the subject was still pregnant at the second follow-up visit, the pregnancy was terminated by vacuum aspiration. If it was doubtful whether the abortion was complete or incomplete, assessment was delayed until the third follow-up visit provided that significant bleeding did not occur. When curettage was necessary between the second follow-up visit and the first menstruation, the outcome of therapy was based on histological examination. If products of conception were found in the curettings, the outcome was classified as incomplete abortion. The duration and amount of bleeding and the occurrence of complications were noted at each follow-up visit and summarized at the last follow-up visit. At that time, the onset and characteristics of the first menstruation were also recorded.

The data were mostly analysed with statistical methods in common use (χ^2-test, t-test). The number of days of sulprostone-induced vaginal bleeding had a positively skew distribution and was therefore log-transformed before analysis. Analysis of variance was then used to examine differences in the duration of bleeding between doses, pregnant and non-pregnant women and treatment outcomes.

Results

Out of the total of 176 women studied, 115 were pregnant whereas 61 (35%) were not pregnant at the time of treatment. As shown in Table 1 the proportion of pregnant women was higher in the low-dose than in the high-dose treatment group ($P<0{\cdot}001$), but the duration of amenorrhoea as well as gravidity, parity, height, weight and age were similar in pregnant and non-pregnant women within and between treatment groups.

The efficacy of sulprostone for termination of pregnancy was dose dependent (Table 2). With the low dose (2×0·25 mg) complete abortion was achieved in 41% compared with in 67% if the high dose (2×0·5 mg) was used ($P<0{\cdot}01$). The figures for incomplete abortion and pregnancy continuation were 28% and 31% with the low dose, and 16% and 18% with the high dose, respectively. If the non-pregnant women were included the frequency of 'successful treatment' (i.e. not pregnant at the second follow-up visit) was 52% for the low dose and 83% for the high dose of the prostaglandin analogue.

Except for 12 of the 79 (15%) women in the low-dose group (3 non-pregnant and 9 pregnant subjects), and 5 of the 97 (5%) women in the high-dose group (2 non-pregnant and 3 pregnant subjects), all subjects, irrespective of whether or not they were pregnant, experienced vaginal bleeding which generally commenced on the day of treatment. The difference between the two treatment groups in the number of women who did not bleed was statistically significant ($\chi^2 = 3{\cdot}94$; d.f. = 1; $P<0{\cdot}05$) but within each group the proportions of 'non-responders' amongst pregnant and non-pregnant women were comparable.

Hardly any of the women treated with the low dose of sulprostone had gastrointestinal side-effects or strong uterine pain requiring an analgesic injection (Table 2). Women given the high dose were more likely to experience vomiting ($P = 0{\cdot}065$, Fisher's exact test) or diarrhoea ($\chi^2 = 4{\cdot}632$, d.f. = 1, $P<0{\cdot}05$).

Except for one non-pregnant subject in the low-dose group and one pregnant subject in both the low- and high-dose group, information was available on the duration of vaginal bleeding in all remaining women (Table 3). Overall, there

Table 1. Number and characteristics of subjects treated with sulprostone

	Dose of sulprostone							
	2×0·25 mg				2×0·50 mg			
Characteristic	Non-pregnant		Pregnant		Non-pregnant		Pregnant	
No. of subjects (%)	15	(19%)	64	(81%)	46	(47%)	51	(53%)
Duration of amenorrhoea (days)	35·1	(2·4)	35·7	(2·0)	36·4	(2·6)	36·4	(2·0)
Gravidity	3·7	(1·9)	4·0	(1·0)*	3·2	(1·8)	3·7	(1·5)*
Parity	1·7	(0·7)	1·7	(1·0)	2·4	(2·7)	1·3	(0·8)
Weight (kg)	57·9	(9·3)	54·8	(10·7)	59·0	(10·4)	56·0	(10·7)
Height (cm)	161	(10)	156	(8)	160	(6)	163	(6)
Age (years)	34·7	(7·2)	31·8	(4·6)	30·1	(6·0)	29·7	(5·8)

* Including the present pregnancy.

Results are means (SD) where appropriate.

Table 2. Efficacy and side-effects of treatment

	Dose of sulprostone			
	2×0·25 mg		2×0·50 mg	
	Non-pregnant	Pregnant	Non-pregnant	Pregnant
No. of women	15	54	46	51
Complete abortion	—	26 (41%)*	—	34 (67%)*
'Successful treatment'†	41 (52%)		80 (83%)	
Incomplete abortion	—	18 (28%)	—	8 (16%)
Pregnancy continuation	—	20 (31%)	—	9 (18%)
Total	79		97	
No. of women with				
Vomiting	0		5	
Diarrhoea	1		10	
Need for intramuscular analgesia	1		4	

* Significantly different between the two treatment groups ($\chi^2 = 6\ 71$, d.f. = 1, $P<0{\cdot}01$).

† Represents women not pregnant at second follow-up visit, i.e. sum of non-pregnant subjects and pregnant women with complete abortion.

was an increase in the duration of bleeding with the higher dose of sulprostone ($F = 6{\cdot}902$, d.f. = 1,152, $P<0{\cdot}01$). Amongst pregnant women, however, dose interacted with treatment outcome, and the increase in the number of bleeding days with dose was present only in those subjects who did not have a complete abortion. There was no difference in the duration of bleeding between pregnant and non-pregnant subjects, but pregnant women with complete abortion bled significantly longer than those who had an incomplete abortion or continuing pregnancy ($F = 65{\cdot}280$, d.f. = 1,97, $P< 0{\cdot}001$).

The amount of bleeding, assessed subjectively by the women in relation to their usual menstrual flow, was generally related to the duration of bleeding. Thus, in both dose groups the proportions of subjects reporting the bleeding to be more or much more than a normal menstruation were comparable amongst non-pregnant and pregnant women (low-dose group: 25% *vs* 31%; high-dose group: 39% *vs* 46%). Likewise, amongst pregnant women, heavier than usual bleeding was reported more often by subjects with complete abortion than by those with incomplete abortion or continuing pregnancy (low-dose group: 54% *vs* 10%, $\chi^2 = 10{\cdot}2$, d.f. = 1, $P<0{\cdot}01$; high-dose group: 53% *vs* 29%, NS). None of the women experienced heavy bleeding necessitating emergency treatment.

The onset and characteristics of the first menstruation were reported for 110 (91%) of the 121

Table 3. Number of days of vaginal bleeding (geometric means, 95% confidence interval and number of subjects)*

	Dose of sulprostone	
	2×0·25 mg	2×0·50 mg
Non-pregnant women	4·9 (3·9, 6·0) ($n = 11$)	5·3 (4·4, 6·4) ($n = 44$)
Pregnant women		
Complete abortion	8·3 (6·6, 10·6) ($n = 25$)	6·7 (5·4, 8·2) ($n = 34$)
Other treatment outcomes	1·8 (1·3, 2·5) ($n = 29$)	3·4 (2·1, 5·4) ($n = 13$)
All women	3·6 (2·7, 4·9) ($n = 54$)	5·5 (4·5, 6·8) ($n = 47$)

* Women without vaginal bleeding ($n = 17$) and those in whom exact duration of bleeding was not known ($n = 3$) have not been included.

women in the 'successful treatment' category. Menses started at approximately the same time, after 4–6 weeks, in both pregnant and non-pregnant subjects of the two treatment groups, and in the majority of women the bleeding was similar to their normal menstruation in respect of duration and perceived amount of blood lost.

Discussion

The development of a medical method of menstrual regulation and termination of very early pregnancy remains an important objective. Apart from being as safe and effective as currently available surgical procedures, such a method should be sufficiently simple to allow its use in non-clinical settings or by the woman herself under supervision. Prostaglandins partially fulfil these requirements provided their use is restricted to the first 2–3 weeks after the missed menstrual period.

Several clinical studies have shown that a complete abortion rate of over 90% can be achieved with some of the recently developed PGE analogues that have increased stability in suppository form or in formulation for intramuscular injection (Takagi *et al.* 1977; Karim *et al.* 1977; Bygdeman *et al.* 1983). Although associated with vomiting, diarrhoea and lower abdominal pain in a significant proportion of women, these analogues have the potential for development into a self-administrable method for termination of early pregnancy in selected women after proper counselling (Rosén *et al.* 1984).

In small randomized studies vaginal administration of prostaglandins has been shown to be equally effective as vacuum aspiration (Lundstrom *et al.* 1977; Smith & Baird 1980; Rosén *et al.* 1984) but it has been difficult to achieve a similar success rate in multicentre trials (WHO Task Force on the Use of Prostaglandins for the Regulation of Fertility 1982). More recently, we have compared the efficacy and side-effects of the intramuscularly administered PGE_2 analogue, sulprostone, with vacuum aspiration in a randomized, multicentre trial in 473 women with a delay of up to 21 days in the expected onset of menses (WHO Task Force on Post-ovulatory Methods for Fertility Regulation 1987). The prostaglandin regimen employed in that study (three injections of 0·5 mg given at 3-h intervals) was found to be equally effective as vacuum aspiration (91% *vs* 94% complete abortions, respectively) but gastrointestinal side-effects and lower abdominal pain requiring intramuscular analgesia were more common in the medically treated subjects.

The aim of the present study was to investigate whether the frequency of these side-effects could be decreased without loss of therapeutic efficacy by reducing the dose of sulprostone, especially if only women with a very early pregnancy (menstrual delay of up to 14 days) were included. To facilitate comparison with the data obtained in our previous trial, the study was carried out by the same group of centres and principal investigators.

The lower doses of sulprostone employed in the present study caused less vomiting, diarrhoea and lower abdominal pain than in our previous trial (29%, 22% and 12% of subjects, respectively), but therapeutic efficacy in terms of the rate of complete abortions achieved also decreased dose-dependently from 91% in our previous study to 67% and 41% in the high- and low-dose groups, respectively, in the present trial. Thus, the sulprostone dose used in our earlier study (3×0·5 mg) appears to represent the minimal, required dose of this prostaglandin when used for menstrual regulation.

Since a delay in the onset of menses rather than a positive pregnancy test was the determining criterion for inclusion in the study, 61 of the 176 treated women (35%) were retrospectively found not to have been pregnant at the time of treatment. In our previous study the proportion of non-pregnant subjects (11%) was significantly lower, presumably because the average duration of amenorrhoea in the women who participated in that study was about 7 days longer than in the present trial. Although the duration of amenorrhoea was similar in the two treatment groups, the percentage of non-pregnant women was found, retrospectively, to have been significantly higher in the high-dose than in the low-dose group. The reason for this unexpected difference is unclear.

As in our previous study, the clinical events following sulprostone administration were essentially comparable in non-pregnant and pregnant women. Both groups of subjects were equally likely to experience treatment-induced vaginal bleeding, and they were also similar in terms of the duration and subjectively perceived abundance of the bleeding. Amongst pregnant women statistical analysis revealed a difference in the number of bleeding days depending on the outcome of therapy. Subjects with complete abortion bled generally longer than those with incomplete abortion or continuing pregnancy, but inter-individual variation was considerable. Thus, for the individual woman, neither the presence or absence of bleeding nor the duration or relative abundance of the bleeding episode represented a predictor of therapy outcome.

Exogenous prostaglandins for termination of pregnancy are potentially capable of causing teratogenic effects as a result of anoxia due to uterine contraction and constriction of the uterine vessels (Iffy & Kaminetzky 1981). In the case of sulprostone, increased rates of fetal malformations have been observed in rats given intravenous doses of 50 μg/kg/day and higher (Schering AG, unpublished results). Therefore, if treatment does not result in complete abortion, the pregnancy should be terminated surgically as was done in the present study.

In conclusion, the data from this and our previous trial suggest that the minimally required total dose of sulprostone when used for menstrual regulation is 1·5 mg (3×0·5 mg). In women with a menstrual delay of up to 21 days this dose is as effective as vacuum aspiration for termination of early pregnancy but, unlike the latter, it is associated with occasional episodes of vomiting or diarrhoea in approximately 20–30% of subjects. A reduction of the sulprostone dose to 0·25 mg or 0·50 mg given twice reduces these side-effects to a significant degree but, at the same time, therapeutic efficacy decreases to a level which is too low to be clinically acceptable. However, recent studies (Bygdeman & Swahn 1985; Cameron *et al.* 1986) indicate that low doses of intramuscular or vaginally administered prostaglandin analogues that cause few or no side-effects are capable of achieving a complete abortion rate of close to 95% in women pretreated with the antiprogestogen RU 486.

Acknowledgments

The prostaglandin analogue, 16-phenoxy-tetranor PGE_2 methyl sulfonylamide (sulprostone) was kindly provided by Schering AG, Berlin. Thanks are due to E. Belsey for statistical advice and to A. Häggblad and J. Marozzi for secretarial assistance.

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A clinical and urodynamic study comparing the Stamey bladder neck suspension and suburethral sling procedures in the treatment of genuine stress incontinence

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Summary. Twenty women with urodynamically proven genuine stress incontinence were randomly allocated to treatment by suburethral sling or Stamey endoscopic bladder neck suspension. Urodynamic assessment was performed before and 3 months after surgery; clinical follow-up is reported up to 2 years. Blood loss was greater, and there were significantly more postoperative complications associated with the sling procedures. The subjective and objective cure rates at 3 months and 2 years were not significantly different between the two procedures. No significant changes in the resting urethral pressure profile were evident, although with both procedures, cure was associated with an enhancement in pressure transmission ratios in the proximal urethra. Detrusor instability occurring for the first time after operation was associated with both procedures; the sling, in addition, induced a significant degree of outflow obstruction, although this was not evident after the Stamey procedure.

The suburethral sling procedure has been widely advocated for the management of recurrent stress incontinence following unsuccessful primary surgical treatment; it may also be appropriate in patients in whom vaginal narrowing makes simpler primary procedures such as the anterior colporrhaphy or colposuspension technically difficult. Numerous sling procedures have been described, with cure rates between 61 and 98%, although the associated morbidity may be considerable (Hohenfellner & Petri 1986). The Stamey endoscopic bladder neck suspension procedure (Stamey 1973) may offer an alternative with fewer complications (Stamey 1980). This procedure has been compared with the colposuspension (Mundy 1983), although not with the sling, which would seem a more appropriate comparison. This paper seeks to compare these two operations in terms of success rates, operative and postoperative complications, and their urodynamic effects.

Patients and methods

Twenty women complaining of stress incontinence, with or without other urinary symptoms, were studied. All underwent a preliminary clinical and urodynamic assessment which included a full medical history, physical examination, bacterial culture of midstream urine specimen, videocystourethrography (Bates *et al.* 1970) or

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Table 1. Age, parity and previous incontinence surgery distribution for the two groups of patients

	Sling	Stamey
Number of women	10	10
Age (years)		
Mean	53·7	57·1
Range	44–62	42–75
Parity		
Mean	3·8+0·5	3·3+0·8
Range	1+0–8+5	1+0–7+2
Previous incontinence surgery		
No. of operations	12	11
No. of patients	6	6

subtracted dual-channel cystometry with simultaneous pressure/flow voiding studies, cystourethroscopy and estimation of urine loss using a short perineal pad test with standard exercise programme (Mayne & Hilton 1987). Urethral pressure measurements at rest and on stress were made using a microtransducer technique described previously (Hilton & Stanton 1983*c*). The diagnosis of pure genuine stress incontinence was confirmed in all patients, and all were considered to be unsuitable for treatment by colposuspension, the author's preferred primary surgical approach, because of post-surgical scarring, or marked atrophic narrowing of the vagina.

Patients were randomized into two groups by means of a random number chart; those drawing odd numbers underwent an abdomino-vaginal suburethral sling procedure using porcine dermis similar to that described by Jarvis & Fowlie (1985); those with even numbers underwent the endoscopic bladder neck suspension operation described by Stamey (1973) and modified by Hilton (1987). All patients received prophylactic subcutaneous heparin, 5000 i.u. every 12 h, and antibiotic cover with ampicillin and metronidazole. All had continuous bladder drainage via a suprapubic catheter for at least 3 days after operation.

All patients were reviewed clinically at 2, 6, 12, and 24 months after operation; urodynamic assessment, including subtracted dual-channel cystometry with simultaneous pressure/flow voiding studies, perineal pad testing, and urethral pressure measurements were repeated at 3 months after operation; perineal pad testing was also repeated at 12 and 24 months after operation.

Because of the small numbers and the wide differences in standard deviations seen between groups for some variables, the data were analysed with non-parametric statistics. For categorical data, McNemar's test or Fisher's exact test was used and for ordinal data Wilcoxon's signed rank test or Mann–Whitney *U*-test was used for paired and unpaired comparisons, respectively.

The methods, definitions, and units conform, where appropriate, to the standards proposed by the International Continence Society (Bates *et al.* 1976, 1977, 1980, 1981).

Results

The mean age of the 20 patients was 56 years (range 42–75) and their mean parity was 3·6+0·6 (range 1+0 to 8+5); the age and parity distribution between the two groups was not significantly different (Table 1). Twelve of the patients

Table 2. Distribution of previous pelvic surgery between the two groups

Patient no.	Sling	Patient no.	Stamey
1	Ant. repair	11	Ant. repair
2	Marshall–Marchetti–Krantz	12	Ant. repair
3	Ant. repair × 2	13	Ant. repair
4	Ant. repair × 2	14	Ant. repair; colposuspension and TAH
5	Vag hyst. and repair; ant. repair; Marshall–Marchetti–Krantz	15	Ant. repair, vag. hyst. and repair; colposuspension
6	Ant. repair × 2; sling	16	Ant repair × 2; colposuspension
7	Radical hysterectomy	17	Radical hysterectomy+radiotherapy
8	Abdominal hysterectomy	18	—
9	—	19	—
10	—	20	—

Ant. repair, Anterior repair; Vag. hyst., vaginal hysterectomy.

Table 3. Urinary symptoms before and at 3 months after surgery in the two groups

	Sling (n=10)		Stamey (n=10)	
	Pre-op.	Post-op	Pre-op.	Post-op.
Frequency (mean no. voids/day)	14·3 (7·4)*	6·2 (2·6)	12·3 (5·6)*	7·1 (5·3)
Nocturia (mean no. voids/night)	1·3 (1·4)	0·8 (0·7)	1·9 (1·6)*	0·5 (0·7)
Stress incontinence (n)	10**	1	10**	1
Sanitary protection (mean no. of pads/day)	5·2 (3·4)*	0	4·3 (3·0)*	0
Urgency (n)	8	5	8	5
Urge incontinence (n)	5	3	6	4
Voiding difficulty (n)	2	4	5	2

Results are mean (SD) values or numbers of patients as appropriate.
Significance of difference between pre- and postoperative findings in each group $^{*}P<0{\cdot}05$, $^{**}P<0{\cdot}001$ (Wilcoxon's signed rank test or McNemar's test as appropriate).

had had between them 23 previous unsuccessful incontinence operations and three others had had other pelvic surgery; the distribution of previous operations between the two groups was closely comparable although the selection of operation was not made on the basis of 'matched pairs' (Table 2).

There were no significant differences in symptoms before operation (Table 3), or cystometric (Table 4) or urethral pressure profilometry variables (Table 5), between the groups of patients.

Operative and postoperative complications for the two procedures are listed in Table 6. Operative blood loss was significantly greater at the time of suburethral sling; retropubic drains were left in place routinely following this operation whereas no drains are left in place at the Stamey procedure; total blood loss, operative and postoperative, was thus also significantly greater with the sling patients. The bladder was opened during dissection at one of the sling operations; this required formal closure, and cathether drainage for 10 days At the time of Stamey procedure the 'Stamey' needle perforated the bladder on two occasions; these simply required removal and replacement, although in one patient continous bladder drainage was maintained for 5 days on account of persistent haematuria. Postoperative pyrexia, defined as a temperature ≥38°C persisting for 24 h, was found in eight of the sling patients but in none of the Stamey patients. Partly as a consequence of these morbidities, and partly as a result of greater postoperative voiding difficulties (Table 7), the mean hospital stay was significantly longer following sling procedures.

Table 4. Cystometric variables before and after surgery in the two groups

	Sling		Stamey	
Variables	Pre-op.	Post-op	Pre-op	Post-op.
Residual volume (ml)	0	3 (4)	5 (7)	1 (3)
First sensation (ml)	300 (197)	266 (147)	210 (65)	301 (143)
Cystometric capacity (ml)	579 (216)	584 (247)	490 (94)	599 (132)
Total pressure rise (cm H_2O) (filling and provocation)	8 (4)	15 (11)	9 (2)	15 (12)
Uninhibited contractions (no of patients)	0	2	0	1
Stress incontinence (no of patients)	10 ***	1	10**	2
Maximum voiding pressure (cm H_2O)	23 (13)	28 (10)	31 (12)	22 (16)
Peak flow rate (ml/s)	29 (8) *	17 (8)†	24 (12)	30 (13)

Results are mean (SD) values.
Significance of difference between pre- and postoperative findings in each group $^{*}P<0{\cdot}05$, $^{**}P<0{\cdot}002$, $^{***}P<0{\cdot}001$ (Wilcoxon's signed rank test or McNemar's test as appropriate)
Significance of difference between postoperative findings in the two groups $^{\dagger}P<0{\cdot}05$ (Mann–Whitney U-test)

Table 5. Urethral pressure profilometry variables before and after surgery in the two groups

Urethral pressure profile	Sling		Stamey	
	Pre-op.	Post-op.	Pre-op.	Post-op.
At rest:				
Total profile length (mm)	31 (8·4)	35 (9·2)	32 (9·2)	35 (7·8)
Functional length (mm)	26 (7·3)	28 (5·5)	26 (5·0)	26 (6·3)
Length to peak pressure (mm)	15 (8·4)	17 (7·3)	17 (2·3)	17 (6·1)
Maximum urethral pressure (cm H_2O)	42 (13·6)	47 (12·7)	40 (14·6)	39 (18·9)
Maximum urethral closure pressure (cm H_2O)	24 (16·3)	26 (14·4)	28 (15·5)	26 (17·8)
At stress:				
Functional length (mm)	5 (3·1)**	18 (5·2)	3 (2·3)**	14 (11·8)
Length to peak pressure (mm)	3 (2·4)*	9 (6·5)	2 (1·8)**	12 (8·4)
Maximum urethral closure pressure (cm H_2O)	5 (4·1)**	26 (23·6)	2 (2·5)**	19 (15·9)
Pressure transmission ratios (%)				
Q1	88 (12·8)	112 (8·4)	75 (10·0)**	107 (9·2)
Q2	81 (8·7)*	113 (11·1)	71 (9·8)**	103 (21·8)
Q3	72 (9·3)*	107 (30·7)†	61 (18·6)	72 (27·1)
Q4	46 (19·0)	57 (27·5)†	38 (14·0)	33 (18·7)

Results are mean (SD) values.

Significance of difference betwen pre- and postoperative findings in each group *$P<0·05$; **$P<0·01$ (Wilcoxon's signed rank test).

Significance of difference between postoperative findings in the two groups †$P<0·05$ (Mann–Whitney *U*-test)

Postoperatively, subjective cure of stress incontinence was found in 90% for both procedures, and no patient in either group needed to wear sanitary protection (Table 3). Symptoms of frequency, urgency, and urge incontinence were reduced to a similar extent by both procedures, although only the reduction in urinary frequency was statistically significant. Voiding difficulty (defined as two or more of the following symptoms: hesitancy, straining to void, poor or intermittent stream, sensation of incomplete emptying, or post-micturition dribbling) was present in more patients after than before the sling operation, in fewer after the Stamey procedure, but neither procedure resulted in a significant change in these symptoms.

An objective cure rate of 90% was found following the sling operation and 80% following the Stamey procedure, at the 3-month reassessment. (Table 4). There were no significant changes in the variables of the filling cystometrogram, although two patients after the sling operation and one after the Stamey procedure were shown to have uninhibited detrusor contractions which were not present pre-operatively. The sling operation resulted in a significant reduction

Table 6. Operative and postoperative complications

Complication	Sling	Stamey
Operative blood loss (ml)	700 (469)*	37 (28·3)
Postoperative wound drainage (ml)	197 (12·9)*	0
Bladder injury (no. of patients)	1	2
Postoperative pyrexia (no. of patients)	8 **	0
Infective complications		
Wound	3 }**	0
Urinary tract	4 }	0
Pulmonary embolus	1	0
Duration of hospital stay (days)	20 (12·9)*	7 (0·3)

Results are mean (SD) values where appropriate

Significance of differences *$P<0·05$; **$P<0·001$ (Mann–Whitney *U*-test or Fisher's exact test as appropriate).

Table 7. Postoperative voiding

	Sling	Stamey
First passed urine (days)	6·8 (4·4)*	3·2 (0·7)
Catheter removed (days)	16·3 (13·9)*	5·1 (0·3)
Adjunctive therapy (no of patients)		
Cholinergic drugs	3	0
Urethrotomy	1	0

Results are mean (SD) values where appropriate. Significance of differences *$P<0·05$ (Mann–Whitney *U*-test).

in peak urine flow rate, along with a small, though not significant, rise in maximum voiding pressure, suggesting a degree of outflow obstruction. Following the Stamey procedure voiding appears to occur with increased efficiency, although the increase in flow rate and reduction in voiding pressure seen were not of statistical significance. The maximum voiding pressures postoperatively were not significantly different between the two procedures, although the peak urine flow rates were significantly higher following the Stamey procedure ($P<0·05$; Mann–Whitney *U*-test). Two years after operation the subjective cure rate was 90% for the sling and 70% for the Stamey procedures; these are not significantly different by Fisher's exact test.

No significant changes in resting urethral pressure profile variables were seen postoperatively (Table 5). Following the sling procedure the maximum urethral pressure appears to be slightly increased (Fig. 1); this reflects an increase in resting intravesical pressure, or impairment of bladder compliance, and not a true increase in urethral closure effect; the maximum urethral closure pressure was unchanged. Both operations resulted in an increase in both length and amplitude of the urethral stress profile; this is due to a significant enhancement in pressure transmission to the urethra; this effect is significantly more marked following the sling procedure in the distal parts of the functional urethral length (Q_3, Q_4) (Fig. 2).

The number of unsuccessful operations in this series is obviously small, and it is difficult to identify reasons for failure. However, the patients in whom the operation failed were older than those whose operations were successful (mean 67·3 years *vs* 53·4 years), and had undergone more previous unsuccessful incontinence operations (7 operations between 3 patients, mean 2·3 each compared with 16 operations between 17 patients, mean 0·9). There were also significant differences in the pre-operative resting maximum urethral closure pressure (Fig. 3).

Discussion

Although numbers are small, these results show that both the abdomino-vaginal suburethral sling and the Stamey endoscopic bladder neck suspension produce acceptable cure rates in difficult cases of genuine stress incontinence. Stamey (1980) reported a 91% cure rate with his procedure, although this was based on a variable follow-up period, and a purely subjective assessment; Mundy (1983) found a 76% objective and 40% subjective cure rate 1 year after the operation. Published success rates for sling procedures vary considerably (Hohenfellner & Petri 1986), although with a similar procedure, Jarvis & Fowlie (1985) found a subjective and objective cure rate of 78% in a similar group of patients.

The two groups investigated were closely comparable for age, parity, previous surgical history, and pre-operative urodynamic findings;

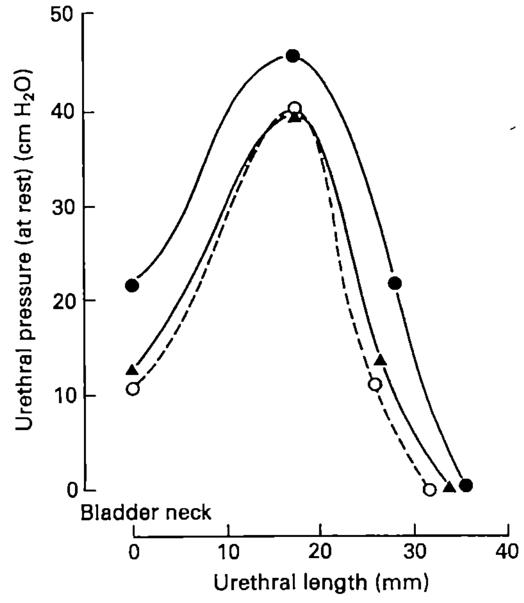

Fig. 1. Mean resting urethral pressure profiles constructed from the mean values of maximum urethral pressure, maximum urethral closure pressure, total profile length, functional length, and length to peak pressure for the following groups: Combined pre-operative data (○), Stamey procedure postoperative (▲), sling procedure postoperative (●).

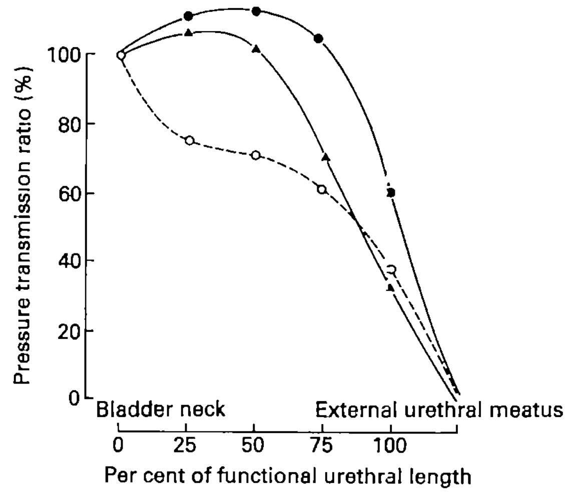

Fig. 2. Mean pressure transmission profiles before and after surgery constructed from mean values of PTR at Q1, Q2, Q3, and Q4 for the following groups: Combined pre-operative data (○), Stamey procedure postoperative (▲), sling procedure postoperative (●).

but operative blood loss and postoperative complications were significantly greater with the sling procedures. The difference in total blood loss reflects the much greater extent of dissection involved in the sling procedure. The high rate of infective complications with the sling operation was also found by Jarvis & Fowlie (1985) who attributed it to the use of the combined abdominal and vaginal approach; but the Stamey procedure also involves a combined approach, and yet has little associated morbidity; the difference in operative time may be relevant to this and to thromboembolic complications.

The relatively poor surgical prognosis associated with low resting maximum urethral pressure has been described previously in relation to both the colposuspension and abdominal suburethral sling (Hilton 1981), although in neither case was it possible to identify any specific urethral closure pressure level below which failure was inevitable, or above which success was guaranteed. In the present study all patients whose surgery was unsuccessful had pre-operative urethral closure pressures <20 cm H_2O; however, five of the patients treated successfully also fell into this range. Ostergard *et al.* (1987) similarly pointed out the poor surgical prognosis associated with low urethral closure pressure, but reported better results from a sling procedure than standard retropubic urethropexy.

The cystometric findings reported point to a significant obstructive effect resulting from the sling operation but not from the Stamey procedure; this has been reported previously following colposuspension (Hilton & Stanton 1983*a*), and an abdominal sling procedure (Hilton & Stanton 1983*b*). In both these previous reports we have concluded that the obstructive effect of these operations was not an important determinant of surgical success, since unsuccessfully treated cases showed a similar degree of compromise to voiding, and some cured patients showed no evidence of obstruction. Previous studies of the Stamey procedure have given variable results; Mundy (1983) reported a significant obstructive influence, whereas Ashken *et al.* (1984) did not; these differences may reflect slight differences in operative technique, or in methods of adjusting suture tension.

In a previous report of the urodynamic effects of an abdominal suburethral sling procedure (Hilton & Stanton 1983*b*), we found a significant increase in total resting urethral profile length; this is not evident in this study, nor was it found by Henriksson & Ulmsten (1978) or Obrink & Bunne (1978). The improvement in pressure transmission ratio after successful treatment by both operations is comparable with our previous

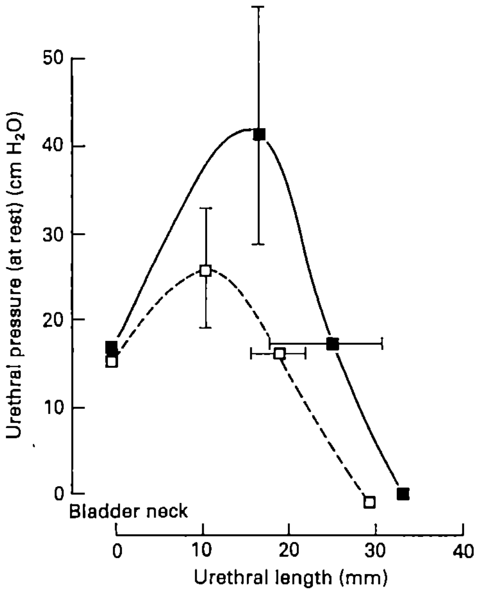

Fig. 3. Mean pre-operative resting urethral pressure profiles in patients with successful (n=17) (■) and unsuccessful (=3) (□) operations (combined for the two procedures). Mean ±1 SD shown for maximum urethral closure pressure and functional urethral length.

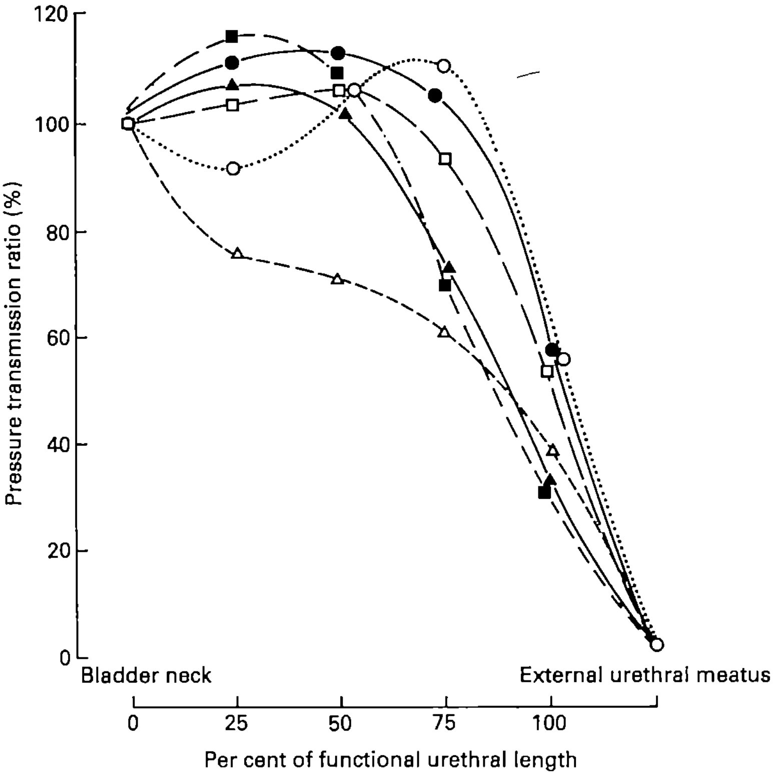

Fig. 4. Mean pressure transmission profiles for symptom-free women (Hilton & Stanton 1983*c*) (○), combined pre-operative data for stress incontinent women (△), and postoperative cases following Burch colposuspension (Hilton & Stanton 1983*a*) (■), abdominal suburethral polypropylene sling (Hilton & Stanton 1983*b*) (□), abdomino-vaginal suburethral porcine dermis sling (●) and Stamey procedure (▲).

findings with colposuspension (Hilton & Stanton 1983*a*) and abdominal sling (1983*b*) and with those of Constantinou *et al.* (1980) with the Stamey procedure. It is possible that bladder neck elevation induced by these operations allows improved efficiency of the pelvic floor reflex and an accentuation of urethral closure by an active means (Heidler *et al.* 1979), although previous studies with the colposuspension suggest that this is unlikely (Hilton & Stanton 1983*a*). The most likely mechanism of cure, and the reason for the improvement in pressure transmission, would seem to be the relocation of the proximal urethra in a high retropubic position, so that intra-abdominal pressure rises cause the bladder base to compress the urethra against the postero-superior surface of the symphysis (Hertogs & Stanton 1985). The distribution of pressure transmission found after Stamey procedure is quite different from that seen physiologically in symptom-free women, and is similar to that reported after colposuspension (Fig. 4); the mechanism of cure is likely to be similar. The more widespread increase in pressure transmission after sling procedures, extending more distally along the urethra, is in keeping with the suggestion of Stanton *et al.* (1985) that the sling may additionally, or alternatively, work by providing a firm support against which the urethra is compressed by any increase in intra-abdominal pressure.

Whilst accepting that the numbers studied are small and the follow-up relatively short, we feel that the results obtained with the Stamey procedure, its short operative time, low associated morbidity, and short hospital stay make it ideally suited to the management of difficult cases of incontinence, especially in the elderly or frail. The negligible effects on outflow resistance mean that it may also be applicable to patients whose voiding efficiency is doubtful pre-operatively, in whom other more obstructive procedures may carry significant risk of subsequent voiding dysfunction. A larger long-term follow-up study is in progress using the Stamey procedure with these specific indications.

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Genital cancer among wives of men with penile cancer. A study between 1958 and 1982

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Summary. Previous studies have suggested an association between penile cancer and cervical cancer but the results have been difficult to interpret. The current study includes 1064 cases of penile cancer reported to the National Swedish Cancer Registry between 1958 and 1980. One matched control for each living case was chosen randomly from the Swedish Population Registry, and for cases who had died, from the National Death Registry. Details about the men, their marriages and each wife or wives were obtained from the population registry in the parish in which the men lived or had died. The personal identification number and name of each wife or wives were matched against the cancer registry. All genital cancers, including 15 cervical cancers, were distributed equally among the wives of the cases and those of the controls. The expected rate of cancers among the population of wives of cases was also calculated and there was no difference between the observed and the expected number of women with cancer. The results did not show an association between penile cancer in men and cervical cancer in their sexual partners.

It has been suggested by many authors that cancer of the cervix and cancer of the penis have a common aetiology (Smith *et al.* 1980*a*; Li *et al.* 1982; Rogan & Milne 1983). The suggestion has been based on anecdotal reports of couples where the woman had cervical cancer and the man had penile cancer (Onuigbo 1984; Goldberg *et al.* 1979; Cartwright & Sinson 1980; Cocks *et al.* 1982).

There is some evidence that human papillomavirus might be a sexually transmitted aetiological factor for both penile and cervical cancer (zur Hausen 1985). It is well known that sexual behaviour constitutes a major risk factor in cervical cancer (Hulka 1982), and it has been suggested that the same applies to penile cancer (King 1980). However, the only reported study that investigated sexual factors in penile cancer found no association with sexual activity (Hellberg *et al.* 1987).

There is a report from China that cervical and penile cancer correlate geographically (Li *et al.* 1982), although this observation has not been confirmed in other parts of the world (Smith *et al.* 1980*b*; Rogan & Milne 1983; Muir & Nectoux 1978).

The most suggestive findings were reported from three studies that dealt with wives of men with penile cancer; all three studies showed an over-representation of wives with cervical cancer (Martinez 1969; Graham *et al.* 1979; Smith *et al.* 1980*a*). However, for a number of reasons these studies are difficult to interpret.

In Sweden almost 100% of all penile and cervical cancers have been reported to the National

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Cancer Registry since 1958. In addition each individual has a personal identification number, thus making it easy to trace them through the Parish Registry, the Death Registry and the National Population Registry.

The incidence of penile cancer in Sweden is 1·3/100 000 per year (National Board of Health and Welfare 1986), which is similar to the figures in the Western World (Persky 1977), but lower than in some parts of the Third World (South America, Uganda, India, China). The annual incidence of cervical cancer in Sweden is 13·2/100 000, which is also comparable to the rest of the Western World.

This study aimed at tracing all wives of men with penile cancer registered during the period 1958–1980, and to compare their cancer frequency with a matched control group and, in a second comparison, to calculate expected frequencies of genital cancer among the wives of the men with penile cancer.

Subjects and methods

Since the start of the Swedish National Cancer Registry in 1958, all malignant tumours in the Swedish population have been notified. Some types of malignant disease, mainly blood cell cancers and those of the central nervous system are under-reported, thus giving a total reporting of all Swedish cancers of 95·5% (Mattsson 1984).

In Sweden the average incidence of penile cancer is 1·3/100 000/year. Median age at confirmation of the diagnosis is 60–65 years (National Board of Health and Welfare 1986). All diagnoses must be confirmed histologically and, in addition, the registry includes information on year of birth, name, address and the hospital and clinic where the cancer was treated. This study includes 1064 men with penile cancer reported between 1958 and 1980.

Table 1. Characteristics of men with penile cancer and matched controls

	Cases	Controls
Number of men	1064	1049
Marital status available(n)	968	968
Year of birth	1904 (15·5)	1904 (15·4)
Ever married n (%)	815 (84·2%)	835 (86·3%)
Age at marriage (years)	30·0 (7·1)	29·8 (6·9)
Year of cancer diagnosis	1969 (13·9)	—

Results are mean (SD) values where appropriate.

Using the Swedish National Population Registry we obtained controls matched for age and area of residence for the 372 men who were still alive where the only inclusion criterion was that they did not have penile cancer. Matched controls for the 692 men who were dead were obtained from the Death Registry of the Sweden Statistics The controls for the dead cases were matched by year of birth, year of death and parish where they died. In this way 1064 controls were obtained. Fifteen of these controls had an incorrect personal identification number and were thus impossible to trace. Geographically matched controls were chosen because the incidence of penile and cervical cancer varies in different parts of Sweden, in particular cervical cancer is more common in urban regions.

The study thus consisted of a total of 2113 men. A letter was written to each parish asking for information about the marital history, including name and personal identification number of the wife or wives and year of marriage and divorce if appropriate. A total of 177 men could not be traced to any parish, distributed equally between cases and controls, thus giving a drop-out rate of 8·4%. Complete marital information was obtained for the remaining 1936 men.

Initially the data for the living and dead men were analysed separately. As there were no differences apart from year of birth between cases and controls, it was decided to combine the data without any subgrouping.

Table 1 gives the mean year of birth of the men, the proportion that had ever been married and the year of cancer diagnosis. There were no significant differences between cases and controls.

In Table 2 marital factors for cases and controls are distributed by first, second and third marriage. No differences appear by the year of birth of the wives or by number of marriages, year of marriage or duration of marriage (year of divorce). Only eight persons were married three times, equally distributed according to year and age between cases and controls, and therefore average figures for these marriages are not shown.

At the beginning of 1958 the mean age of the

Table 2. Marital factors in men with penile cancer and matched controls

	Cases (n=968)	Controls (n=968)
Year of birth of wives		
1st marriage	1907 (16·0)	1907 (15·8)
2nd marriage	1916 (14·1)	1915 (16·9)
3rd marriage	1918 (25·7)	1921 (4·0)
Number of marriages		
1 n (%)	815 (84·2)	835 (86·3)
2 n (%)	48 (5·0)	54 (5·6)
3 n (%)	5 (0·5)	3 (0·3)
Year of marriage		
1st marriage	1934 (15·7)	1934 (15·7)
2nd marriage	1956 (12·4)	1953 (16·3)
Year of divorce		
1st marriage	1972 (13·9)	1972 (14·2)
2nd marriage	1976 (8·0)	1973 (14·5)

Results are mean (SD) or n (%) as appropriate.

wives of cases was 47·8 years (SD 15·3) and of the controls 48·1 years (SD 15·0). The Cancer Registry was searched to identify those women who had had cancer diagnosed between 1958 and 1982. The women who were still alive in 1982 were aged 66·5 (SD 13·5) and 66·9 (SD 13·1) years, respectively. Of all wives, 1648 were alive in 1958, with no difference between case and control groups.

In 1986, 1107 women of the first marriage, 74 women of the second marriage and all eight women of the third marriage were alive. Of those who were dead of the first marriage, the wives of the cases had a mean age at death of 71·6 years (SD 13·0, n=521) compared with 70·8 years (SD 13·8, n=485) for the wives of the controls, and the corresponding ages for wives of the second marriage were 69·2 years (SD 11·4, n=15) and 66·8 years (SD 17·7, n=13).

Finally, the expected frequency of cancer in the wives of the cases was calculated by matching age and the years 1958–1982 (at this point the Cancer Registry was updated for 2 years) with the publication *Cancer Incidence in Sweden* (National Board of Health and Welfare) for each year. This processing was done by UMDAC (Umeå Computer Central) using a specially designed computerized analysis.

Results

Altogether among the 1760 wives 238 were found who had cancer; 131 of them were wives of cases and 107 were wives of controls; there was no significant difference between the case and control groups. The expected total frequency of cancers for wives of cases was 131.

Table 3 shows the frequency of female genital cancers and a comparison is made with that in controls and the expected frequency. The expected number of invasive cervical cancers was 5·5 compared with 8 observed for the cases and 7 for the controls. The difference is not statistically significant.

For the other female genital cancers there were also no statistically significant differences between cases, controls or expected frequency. The mean age for all women with genital cancers was 60·7 years in the cases and 59·0 years in the control group.

Each of two men with penile cancer who had been married more than once had two wives who both had cancer. One man had one wife with cancer of the colon and a second wife with cancer of the rectum. The other man had a wife with cervical cancer and a second wife with cancer of the pleura.

Discussion

This study did not confirm the findings of previous investigations, which showed an increased risk for cervical cancer among wives of men with penile cancer. Analysis by matched pairs would not alter the conclusions.

Ideally all sexual partners, not only the wives, should have been traced, but this was impossible as the parish registries have no information about extramarital relations. The ages of both the men and the women in this study suggest that they initiated their sexual relations at a time when most sexual relationships occurred within marriage.

A possible source of bias in this study is the fact that only genital cancers diagnosed between

Table 3. Distribution of genital cancers in wives of men with penile cancer and in a control group, and the expected numbers of genital cancers

	Cases	Controls	Expected
Cervical cancer	8	7	5·5
Endometrial cancer	5	7	6·8
Ovarian cancer	7	5	7·5
Vulvar cancer	1	2	1·3

1958 and 1982 were known. However, there was no increased mortality, shorter marriages or more remarriages among the cases compared with the controls. In 1958 the wives of the cases and those of the controls had a mean age of 47·8 and 48·1 years respectively. The median age for the diagnosis of cervical cancer in Sweden is 50–54 years, and this study would thus cover the onset of most of the cervical cancers occurring both in the cases and controls. Cervical cancers occurring before 1958 are of course missed in this study, but considering the equal mortality in general, and the equal mortality before 1958 in particular, it is unlikely that there was an increased frequency in cervical cancer among younger women married to men who developed penile cancer.

Martinez (1969) reported a series of 889 men with penile cancer in Puerto Rico. Eight wives in this group had cervical cancers compared with none in a control group. The absence of any women with cervical cancer in the control group was somewhat surprising, since cervical cancer is very common in Puerto Rico with an annual incidence of 38/100 000 (Martinez 1969). The fact that all but two of the women with cervical cancer were diagnosed after the penile cancer in their partner gives rise to the suspicion that these women received closer surveillance for cervical cancer than the general population.

Another study (Graham *et al.* 1979) included 256 men with penile cancer in New York State between 1958 and 1964. The drop-out rate was 11% and there was no control group. Six cases of cervical cancer were found compared to 1·85 expected. The lack of a control group and the suspicion that men with penile cancer might be over-represented in lower socio-economic classes, in the same way as are women with cervical cancer, make the results difficult to interpret.

The third study (Smith *et al.* 1980*a*) included 1022 men who had died from penile cancer between 1964 and 1973. More than 30% of these men were excluded from the study, either because it was impossible to trace their wives since their records could not be located, or they were divorced or widowed, or because their marital status was unknown. Thus 711 men were included, all were married and their wives were checked in the mortality registry. There was no control group and the observed number of deaths was compared to a calculated expected number of deaths from cervical cancer. The authors found 11 deaths from cervical cancer against the expected number of 3·9. The high drop-out rate and the lack of a control group also make this study somewhat difficult to interpret.

In one study, cervical biopsies were taken from wives of 80 men with penile cancer. No cancer and only one mild dysplasia was found (Reddy *et al.* 1977).

The present study was expected to confirm that wives of men with penile cancer are at high risk of developing cancer, but it has not done this. There is, however, clear evidence that a group of high-risk males exists (Kessler 1977), although they may not necessarily be men who run a greater risk of having penile cancer. It has recently been shown that male sexual partners of women with cervical intraepithelial neoplasia (CIN) have a high frequency of human papilloma-virus (HPV) infection of the glans penis (Levine *et al.* 1984). It has also been shown that 36% of the men infected with HPV 16 are the sexual partners of women with cervical HPV infection or CIN. These men may not necessarily develop penile cancer, though they have an increased frequency of Bowen's disease and their partners are at high risk of developing cervical neoplasia (Campion *et al.* 1985).

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A comparison of single-dose oral fluconazole with 3-day intravaginal clotrimazole in the treatment of vaginal candidiasis

REPORT OF AN INTERNATIONAL MULTICENTRE TRIAL

Summary. A total of 369 women with clinical and mycological evidence of vaginal candidiasis received treatment, after random allocation, with either a single oral 150-mg dose of fluconazole (188 women) or 200 mg of intravaginal clotrimazole given daily for 3 consecutive days (181 women). They were assessed at 5–16 days and again at 27–62 days after treatment. *Candida* species were completely eradicated from the vagina in 72% of the fluconazole group and in 62% of the clotrimazole group at the long-term assessment ($P=0 \cdot 07$). Favourable clinical responses were obtained in 99% of the fluconazole group and in 97% of the clotrimazole group at the short-term assessment and in 93% and 84% respectively at the long-term assessment when there was a significant advantage for fluconazole treatment ($P=0 \cdot 02$). Symptoms in patients receiving fluconazole were relieved more rapidly ($P<0 \cdot 001$). Treatment-related side-effects were few and minor in both groups. It is concluded that treatment of vaginal candidiasis with fluconazole, as a single oral dose, was more effective in the long term, relieved symptoms more rapidly, and was as safe as treatment with intravaginal clotrimazole.

Vaginal candidiasis, usually due to infection with *Candida albicans,* is a common and worldwide problem. With symptoms varying from a mildly irritating discharge to severe perineal discomfort and dyspareunia, it can seriously disrupt the life of the affected patient.

For many years treatment has relied on the topical use of pessaries, creams, or tablets; this can be messy and aesthetically displeasing and both the woman and her sexual partner may report local irritation, burning, and frequency of micturition. Consequently, compliance with treatment may be poor. Moreover, many women stop treatment as soon as their symptoms have cleared, but before eradication of the yeast has been confirmed mycologically. Relapse or reinfection is not uncommon since the rectum may still be harbouring the yeast, and this has been shown to be an important factor in recurrent infection (Miles *et al.* 1977).

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When oral ketoconazole treatment was introduced early in the 1980s it had to be given over a number of days (van der Pas *et al.* 1983; Cauwenbergh & de Doncker 1986) and was not entirely free of side-effects (Pont *et al.* 1982; Hawkins 1984). Fluconazole, a new bis-triazole antifungal agent (Richardson *et al.* 1985), which is well absorbed orally and has a long systemic half-life (about 25 h) (Brammer & Tarbit 1987), has the potential to overcome these problems. This international multicentre trial was therefore designed to compare the efficacy of a single oral dose of fluconazole with that of a standard topical clotrimazole regimen in the treatment of women with acute vaginal candidiasis. The primary criteria of efficacy were to be the mycological response (eradication of *Candida* from the vagina) and clinical response (relief of symptoms and elimination of signs of the vaginal infection) assessed at 1–2 weeks and approximately 6 weeks after treatment. Information on the speed of symptomatic relief was also to be obtained.

Patients and methods

Ethical approval for the protocol was obtained from an international ethical review committee (Faccini *et al.* 1984) and, where necessary, from the relevant local ethics committees of the individual participating centres.

Patients were entered into this multicentre study at 16 separate centres in Europe. They were allocated in blocks of four according to a computer-generated randomization list at each participating centre to receive either fluconazole (three 50-mg capsules as a single oral dose, preferably with a meal) or clotrimazole (one 200-mg tablet inserted intravaginally on each of 3 consecutive days).

Criteria for inclusion

Women aged 18 years or over with characteristic signs and symptoms of vaginal candidiasis were included in the study. The clinical diagnosis was confirmed initially by the presence of pseudohyphae (pseudomycelia) seen with the light microscope and subsequently confirmed by culture. The patients were symptomatic with, as a minimum, either vaginal pruritus or burning. They gave their informed consent to participate in the study.

Criteria for exclusion

Apart from pregnant or lactating women, patients were excluded if they had any clinically relevant associated disease or were known to have impaired hepatic or renal function. Women with venereal disease, chlamydial infection, trichomoniasis, or non-specific vaginitis were also excluded, as were those using any other antifungal treatment, any topical vaginal or vulval preparation, or who were known to be sensitive to azole-containing drugs.

Efficacy assessment

Mycological examination was performed on two high vaginal swabs, one was inoculated in transport medium for trichomonal examination and the other was transported dry for culture on Sabouraud chloramphenicol agar, or its equivalent, and examination after 48 h incubation. A smear was also examined by direct microscopy at the same time as the vaginal swabs were obtained. These examinations were undertaken at baseline and at short- and long-term assessments. Mycological eradication was defined as both a negative culture and negative microscopy for *Candida* when assessed after treatment. (If other pathogens, specifically *Trichomonas vaginalis, Gardnerella vaginalis* or *Chlamydia* species, were also detected before treatment, the patient was excluded from the efficacy analysis.) The mycological assessment was done in blinded fashion without knowledge of the treatment given.

Symptoms and signs of the vaginal infection were recorded before treatment. The clinical assessment of response was made by both investigator and patient at 5–16 days after the first dose (short-term assessment) and again at 27–62 days (long-term assessment). Each symptom and sign was assigned a score by the investigator on a 0–3 scale: 0=absent; 1=mild; 2=moderate; 3=severe. Clinical assessments were subdivided into cured, improved, and failed. If the patient was either cured or improved, the clinical response was regarded as favourable.

Patients were asked about the speed of their response, and the estimated times from the start of treatment to the onset of relief and the complete relief of symptoms were recorded. At one centre most of the patients treated with fluconazole were asked to state whether they preferred oral or local treatment and their responses were recorded.

Safety assessment

Side-effects. These were recorded at both assessments and any side-effects that occurred during therapy and the subsequent 11 days were assessed for their possible cause–effect relation to treatment.

Laboratory investigations. Routine haematology and a standard range of hepatic and renal function tests were made at the baseline and short-term assessment.

Statistical analysis

The aim was to assess the efficacy results for approximately 350 patients (175 in each treatment group). This would give the study 90% power to achieve a statistically significant difference ($P \leq 0{\cdot}05$) between an 85% mycological cure rate for fluconazole and 70% for intravaginal clotrimazole (a typical value in published studies) at long-term assessment.

Logistic regression analysis was used to test for the significance of any differences in the proportion of patients cured mycologically or responding clinically at both the short- and long-term assessments. The possibility of the proportion of patients cured or responding clinically in each treatment group differing between centres was also investigated by a test for a centre by treatment interaction using the logistic technique. Because of the relatively small number of patients in each of the 16 centres they were merged into three geographical regions: Nordic countries, France, and Germany/The Netherlands. In addition to the primary efficacy indices, a further two variables, time to onset of relief and time to complete relief of symptoms, were also analysed, using a Wilcoxon rank sum test adjusting for regional differences.

Results

A total of 372 patients was entered into the study at 16 separate centres in six countries (Denmark, Finland, France, Germany, Norway and The Netherlands), although only 369 different patients received treatment. This was due to three patients being entered twice: only the first treatment in each case was analysed for efficacy, but both courses of treatment were assessed for side-effects and safety. Of the 369 patients, 188 were allocated to fluconazole treatment and 181 to clotrimazole. The two treatment groups were comparable in terms of age, weight, infection characteristics and factors possibly predisposing to infection (Table 1).

Most of the patients with confirmed vaginal candidiasis had *Candida albicans* cultured at baseline. Eleven patients in the fluconazole

Table 1. Patient details and factors possibly predisposing to vaginal candidiasis

Characteristic	Treatment group Fluconazole (n=188)	 Clotrimazole (n=181)
Mean age (years)	32·1	30·6
Mean weight (kg)	60·1	59·4
Mean severity score of present infection at baseline	6·1	5·9
Previous episodes		
None	107	102
One or more	80	79
Not specified	1	0
Method of contraception		
None	70	71
Oral	66	60
Intrauterine device	44	39
Barrier	7	9
Other	1	2
Antibiotic treatment	18	25
Corticosteroid treatment	3	0
Diabetes mellitus	1	1

group and 16 in the clotrimazole group had *Candida* species other than *C.albicans* isolated at baseline. There were 28 patients who were entered into the study and received their allocated treatment but who did not fulfil the specified criteria for the diagnosis of vaginal candidiasis (either they lacked symptoms or were without mycological confirmation of infection). These patients were automatically excluded from all efficacy analyses without reference to their treatment group allocation, but they were assessed for side-effects and safety. The numbers of patients excluded from the efficacy analyses, together with the reasons for exclusion, are shown in Table 2. These were broadly similar for both treatment groups.

The mycological and clinical responses to treatment at both assessment times are summarized in Table 3. Complete vaginal eradication of *Candida* species was achieved in a slightly lower proportion of patients than anticipated in both treatment groups, but there was an advantage in favour of fluconazole at both assessment times which approached statistical significance (P=0·07) at the long-term assessment. A favourable clinical response was observed in nearly all patients in both treatment groups at the short-term assessment, but by the long-term assessment more relapses or reinfections had occurred in clotrimazole-treated patients, resulting in a statistically significant advantage for fluconazole at this time (P=0·02). Most of the patients with favourable clinical responses were considered completely cured but a small number of patients in both treatment groups had persisting, but minor, signs and symptoms of infection. The proportion of patients in this category was similar in each treatment group at both times of assessment and did not always correlate with the presence of *Candida* species in the vagina.

From the analysis of response by region there was no statistically significant variation in either the mycological or clinical response to treatment by geographical region.

The speed of response to the study treatment was ascertained by asking each improved woman first when she started to feel some relief of symptoms and second when all symptoms had completely resolved. Responses to the first question were obtained from 350 women and to the second from 318 women. Most of the responses were given in terms of days. When analysed by treatment group, the median times to the start of symptomatic relief were 1 day for fluconazole and 2 days for clotrimazole, and the corresponding times to complete symptomatic relief were 2 days and 3 days. Both differences were highly significant (P<0·001), indicating a more rapid clinical response with oral fluconazole treatment than with intravaginal clotrimazole.

At one centre (at which 90 patients were

Table 2. Exclusions from efficacy assessments

		Number of patients	
Assessment	Reason for exclusion	Fluconazole (n=188)	Clotrimazole (n=181)
Short-term (5–16 days)			
Clinical	Inadequate evidence of infection	12	16
	No data in specified period	4	4
	Data not assessable	0	2
		Total 16	Total 22
Mycological	Inadequate evidence of infection	12	16
	No data in specified period	4	4
	Inadequate mycology	3	0
		Total 19	Total 20
Long-term (27–62 days)			
Clinical	Inadequate evidence of infection	12	16
	No data in specified period	24	30
		Total 36	Total 46
Mycological	Inadequate evidence of infection	12	16
	No data in specified period	13	17
	Inadequate mycology	3	3
		Total 28	Total 36

Table 3. Summary of efficacy results

Assessment	No. of patients/No. assessable Fluconazole (n=188)	 Clotrimazole (n=181)	Significance (P value)
Short-term (5–16 days)			
Mycologically cured	143/169 (85%)	131/161 (81%)	0·43
Favourable clinical response	171/172 (99%)	154/159 (97%)	0·12
Long-term (27–62 days)			
Mycologically cured	115/160 (72%)	90/145 (62%)	0·07
Favourable clinical response	141/152 (93%)	113/135 (84%)	0·02

entered into the study) the 45 fluconazole-treated patients were asked if they preferred the oral treatment to the more conventional intravaginal forms of treatment. Of the 38 responses recorded, 25 expressed a preference for oral treatment and 13 had no particular preference. No patient expressed a preference for intravaginal treatment.

Both treatments proved to be well tolerated and safe. Only eight women in the fluconazole group and nine in the clotrimazole group reported side-effects (Table 4) which were mostly rated as mild. None was rated as severe.

Most patients were assessable for drug safety. Abnormal results in the laboratory safety tests which may have been related to treatment were recorded for 14 of the 178 assessable patients who had received fluconazole and for 17 of the 173 assessable patients who had received clotrimazole (Table 5). None of the abnormalities was major or gave rise to any clinical concern for the well-being of the patients involved. Since the magnitude and distribution of the abnormal indices was similar in both groups, and since it is unlikely that a topically applied preparation such as intravaginal clotrimazole would affect these indices significantly, it is probable that the abnormalities recorded represent the normal day-to-day variation in a relatively healthy patient sample of this size.

Discussion

Both treatments proved very effective in the treatment of vaginal candidiasis in this study sample. The study was of open design as the two treatments being compared were administered by different routes. But the mycological investigations were conducted and analysed without knowledge of the treatment received and the results were consistent with the clinical observations except that a proportion of the patients continued to harbour vaginal yeasts in the absence of evident infection. It is probable, therefore, that the efficacy advantage seen with fluconazole at the long-term assessment is a real one. Long-term cures are of particular clinical importance as vaginal candidiasis owes much of

Table 4. Summary of side-effects

Side-effect	Number of patients reporting side-effect Fluconazole group	 Clotrimazole group
Diarrhoea	0	1
Vomiting	1	0
Abdominal pain	3	1
Perineal pain	0	5
Vaginal haemorrhage	0	1
Thirst	1	0
Nervousness	1	0
Fatigue	2	0
Unspecified pruritus	0	1
All side-effects	8	9

Table 5. Summary of laboratory test abnormalities

Abnormal factor	Number of patients with abnormality	
	Fluconazole group	Clotrimazole group
Platelets	1	0
Platelets, WBC count and alkaline phosphatase	1	0
Platelets and WBC count	0	1
WBC count	3	10
WBC count, SGOT and SGPT	1	0
WBC count and SGOT	1	0
WBC count and CPK	0	1
Serum bilirubin	2	2
SGOT	1	0
SGOT and SGPT	0	1
SGPT	0	1
CPK	4	1
All abnormalities	14	17

its morbidity to the frequency of relapses or recurrences after conventional topical therapy.

It has been suggested that the rectum is an important reservoir of *Candida* species which may predispose to relapses or recurrence of infections. In a study of 98 young women with recurrent vaginal candidiasis, Miles *et al.* (1977) found that if *Candida albicans* was cultured from the vagina it was always culturable from the stool. Conversely, if the organism was not isolated from the stool it was never found in the vagina. On the basis of these observations they concluded that a cure of vaginal candidiasis would not be possible without previous eradication of *Candida* species from the gut. It is possible, therefore, that the superior long-term efficacy of fluconazole in the present study may reflect a concomitant reduction of rectal yeast colonization Intravaginally administered antifungal agents are absorbed to only a very limited extent and are unlikely to influence rectal colonization. Although rectal yeast colonization was not monitored in this study, Kutzer *et al.* (1989) demonstrated that a single oral dose of fluconazole did eliminate rectal yeasts from about half the colonized patients and the rate of vaginal candidiasis relapse in these patients was much lower than that in patients who remained colonized.

Another possible explanation for relapse of vaginal infection is that the yeast is not completely eradicated from the vagina. A single negative culture of the vaginal lumen does not guarantee that the organism has been totally eliminated (Odds 1982). There is evidence that *Candida* species may invade the epithelial cells (Garcia-Tamayo *et al.* 1982), and O'Connor & Sobel (1986) noted that early recurrence was more likely to be associated with the same strain or species of *Candida* than was later recurrence ≥6 months after the initial infection. A systemically effective agent such as fluconazole would probably eliminate invasive *Candida* from vaginal tissue more efficiently than a topically applied agent.

In addition to the efficacy advantage indicated in our study, oral treatment with a single dose of fluconazole had a number of other advantages over topical therapy which were appreciated by the patient. The symptoms were relieved more rapidly, and among those patients questioned there was a clear preference for oral treatment, as has been reported elsewhere (Miller *et al.* 1984; Bisschop *et al.* 1985; Tooley 1985). Being used as a single dose also ensured compliance, another factor which is variable with the use of multiple-dose topical regimens.

We conclude that oral treatment with a single 150-mg dose of fluconazole is an effective, well-tolerated and safe new therapy for vaginal candidiasis which may have a number of advantages over conventional forms of treatment.

Acknowledgments

The authors wish to thank Mr N. F. Baker for the statistical analyses.

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Tuberculous meningitis in pregnancy

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Summary. Four women with tuberculous meningitis in association with pregnancy are described to illustrate both the serious nature and varied presentation of this condition. Mortality or neurological morbidity may occur more frequently during pregnancy, but in general correlate closely with delay in diagnosis and initiation of appropriate therapy. Treatment often needs to be started empirically, and neurosurgical intervention may prove life saving.

Tuberculosis of the central nervous system is the gravest form of infection with *Mycobacterium tuberculosis* (Kennedy & Fallon 1979). In cerebral tuberculosis, infection is usually diffuse (meningitis or meningo-encephalitis) but is occasionally focal (tuberculoma). It may be confined to the central nervous system (focal reactivation) or be part of a disseminated process (meningo-miliary disease).

Pathologically there is a hypersensitivity reaction by cerebral tissue to the presence of tubercle bacilli. These require special staining (e.g. Ziehl-Neelsen), are usually very few in number and therefore difficult to demonstrate in cerebrospinal fluid (CSF) This cerebral 'Mantoux reaction' develops often only gradually, resulting in an insidious clinical onset which is both characteristic and distinct from acute meningitis. The CSF findings are often 'atypical' and may further complicate the diagnosis.

The adverse prognosis of tuberculous meningitis in pregnancy was initially reported in a small series of six women of whom two died (Stephanopolous 1957). In another series, D'Cruz & Dandeker (1968) reported similar findings, particularly the common presentation in later pregnancy and the poor outcome where delivery occurred before diagnosis.

Since 1960, 56 cases of tuberculous meningitis have been admitted to Ruchill Hospital, Glasgow, and have been analysed in detail previously (Kennedy & Fallon 1979). This unselected series showed the importance of early recourse to chemotherapy, often empirically based, and it emphasized the value of both steroid therapy and neurosurgical intervention. The present report describes four women with tuberculous meningitis in pregnancy.

Case reports

The clinical details of the four patients are summarized in Table 1. Three were Caucasian, and one (no.2) was an immigrant from Pakistan who died 6 days after admission, having given birth to an infant at 28 weeks gestation who survived.

All the patients had been unwell for some time before admission to Ruchill Hospital. Two had consulted their general practitioners on several occasions before referral and one had been referred to a dermatologist with erythema nodosum. The other two women (nos 1 and 4) were transferred from maternity hospitals subsequent to delivery, but in no patient was tuberculous meningitis suspected before admission.

All had complained of recurrent headaches. Three had a history of a protracted cough, and two complained of persistent nausea and vomiting. In addition, three patients described intermittent fever and night sweats.

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Table 1. Clinical features and outcome in four pregnant women with tuberculous meningitis

Patient	Age (years)	Duration of symptoms before presentation (months)	Presentation	Outcome	
				Maternal	Fetal
1	28	1	Transferred in a confused state 24 h after delivery at 28 weeks	Full recovery	Neonatal death
2	23	3	Presented at 28 weeks; preterm labour next day	Died after 6 days	Alive
3	25	2	Transferred 2 weeks after preterm delivery at 28 weeks	Residual hemiplegia	Neonatal death
4	35	1	Presented 3 weeks after miscarriage at 12 weeks	Full recovery	—

Two patients had impaired consciousness on admission; one also had a left hemiparesis. At presentation only two had detectable nuchal rigidity and one was afebrile. A chest X-ray taken on admission showed miliary disease in three, and changes of old tuberculosis in the fourth. The Mantoux tests performed in two patients were both negative. All had a lumbar puncture within 24 h of admission, and the results are shown in Table 2. This confirmed the diagnosis in three patients, but patient no. 4 required three lumbar punctures. In only one patient (no. 2) were the CSF findings typical of tuberculous meningitis, that is a lymphocytic cell response with low glucose and high protein.

All patients began chemotherapy within 24 h of admission. Three patients received isoniazid, para-amino salicylic acid (PAS) and streptomycin, whereas patient no. 2, who presented in 1981, received modern therapy consisting of isoniazid, rifampicin and ethambutol. All received pyridoxine to prevent isoniazid-induced peripheral neuritis, and, in addition, prednisolone 30 mg per day. Cultures of *Mycobacterium tuberculosis* were obtained in two patients, and were fully sensitive to the drugs used.

Only one patient made an uncomplicated recovery (no. 4). Neurological signs developed in the other three as follows. Patient 1, drowsy on admission with a left hemiparesis, progressed to a hemiplegia, but eventually made a full neurological recovery. Patients 2 and 3 were transferred for neurosurgical assessment. In patient 2, disorientation on admission progressed to increasing drowsiness and a left hemiplegia within 24 h, followed by coma and death 6 days after initial presentation despite intensive support; computerized tomography (CT) revealed a right temporofrontal infarction due to vasculitis. In patient 3 there were no focal signs on admission, but a right-sided hemiplegia developed after 4 days of treatment although a CT scan was normal, and the patient was left with a residual hemiplegia.

Discussion

The earlier reports (Stephanopolous 1957; D'Cruz & Dandeker 1968) of an adverse outcome of tuberculous meningitis in pregnancy are confirmed by our experience in this small series with one maternal death and one severe residual hemiplegia. The common presentation around

Table 2. Cerebrospinal fluid results

Patient	No. of samples	Cell count and predominant type	Glucose* (mmol/l)	Protein† (g/l)	Micro	Culture
1	1	116/mm³ polymorphs	4·0	1·0	+	+
2	1	442/mm³ lymphocytes	0·9	6·4	+	+
3	1	196/mm³ polymorphs	NA	NA	+	−
4	3	87/mm³ lymphocytes	2·5	0·6	+	−

*Normal >2·5 mmol/l; CSF glucose is normally 2/3 plasma glucose.
†Normal 0·1–0·4 g/l.
NA, Not available.

28 weeks gestation and the poorer prognosis of those presenting after preterm delivery is confirmed.

A poor outcome is likely if diagnosis is unduly delayed and the patient is allowed to deteriorate before treatment starts. All four patients had been symptomatic for some time before presentation. Such delay has been shown to correlate closely with outcome (Fallon & Kennedy 1981), as does the degree of neurological impairment at commencement of treatment. Delay results partly from the non-specific and protean nature of the condition and partly because of a lack of modern medical awareness of tuberculosis. Furthermore, CSF results may be confusing because of 'atypical' features and because tubercle bacilli are often not seen. Therefore empirical chemotherapy is frequently justified because it is life-saving and does not seem to obscure subsequent confirmation of the diagnosis (Kennedy & Fallon 1979). Treatment should consist of triple therapy as described in our second patient. In the seriously ill patient, pyrazinamide should also be used (Chambers *et al.* 1984), because of its excellent CSF penetration and bactericidal action (Ellard *et al.* 1987). The collaboration of a tuberculosis specialist should be sought.

An increasing proportion of tuberculous meningitis in Britain occurs in immigrants from areas with a high prevalence of tuberculosis (Tang & Swash 1985). Screening such women for evidence of tuberculosis during pregnancy by Mantoux testing and chest radiography has been advocated (McIntyre *et al.* 1987). Certainly with clinically manifest disease our experience confirms the usefulness of a chest X-ray. However, we believe a high index of suspicion is important for diagnosis because of the enigmatic presentation of this condition.

Though currently a rare cause of maternal mortality in Britain, the spread of human immunodeficiency virus (HIV) means serious infections including tuberculosis may pose an increasing threat to the pregnant population (Centers for Disease Control 1987)

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Peritoneal keratin granulomas from transtubal spread of endometrial carcinoma with squamous metaplasia (adenoacanthoma). Case report

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Case report

A 53-year-old unmarried woman, postmenopausal for 3 years, presented to another hospital in 1985 complaining of vaginal bleeding. She had never been pregnant and denied ever having had coitus. She was admitted for examination under anaesthesia, which revealed a normal vagina and cervix with an anteverted uterus. Curettage produced insufficient tissue for diagnosis. Seventeen days later she was admitted again with vaginal bleeding which was attributed to infection and treated with antibiotics. The bleeding subsided over the following few days.

In February 1987 she presented to the Elizabeth Garrett Anderson Hospital, again complaining of profuse vaginal bleeding. This had started 2 months earlier with two episodes lasting several days each, followed by intermittent bleeding since. She also stated that, following her curettage in 1985, she had had vaginal bleeding for 6 months associated with loin pain and haematuria. At this presentation she felt unwell but had no urinary symptoms. On vaginal examination she had a normal vulva, vagina and cervix, with bleeding through the external os. The uterus was 6–8 weeks size. Rectal examination was normal.

A cervical smear showed abnormal endometrial cells, and ultrasonographic examination of the pelvis showed a bulky uterus with thickened endometrium of irregular density. A dilatation and curretage was performed and a histological diagnosis of well-differentiated endometrial adenocarcinoma with squamous metaplasia was made.

At operation a week later a small amount of free fluid was found in the pouch of Douglas; this was aspirated and submitted for cytological examination. There was also a nodule of tissue, 1 cm in diameter, lying free in the pouch of Douglas. Pelvic adhesions were present, tethering the left side of the uterus to the bladder anteriorly and to the rectum posteriorly. A hysterectomy with bilateral salpingo-oophorectomy was performed. Biopsies of right and left common iliac lymph nodes were performed. Other abdominal organs were found to be normal. She made an uneventful postoperative recovery. At follow-up 2 months later she was well, with good healing of the wound.

Pathological findings

The uterus measured 8 cm in length, 5 cm laterally, and 4 cm antero-posteriorly. The entire endometrial cavity, including both cornua, was filled by papillary tumour tissue. There was no apparent infiltration of the myometrium; the cervix and vaginal cuff were normal.

The nodule from the pouch of Douglas was 1 cm in diameter, attached to a thin pedicle. There was an enlarged right common iliac lymph node, but no obvious nodes were present in the fibrofatty tissue from the region of the left common iliac lymph nodes.

The endometrium was replaced by a well-differentiated adenocarcinoma with foci of squamous epithelium distributed throughout the tumour (adenoacanthoma) (Fig. 1). There was neither evidence of myometrial invasion, nor of

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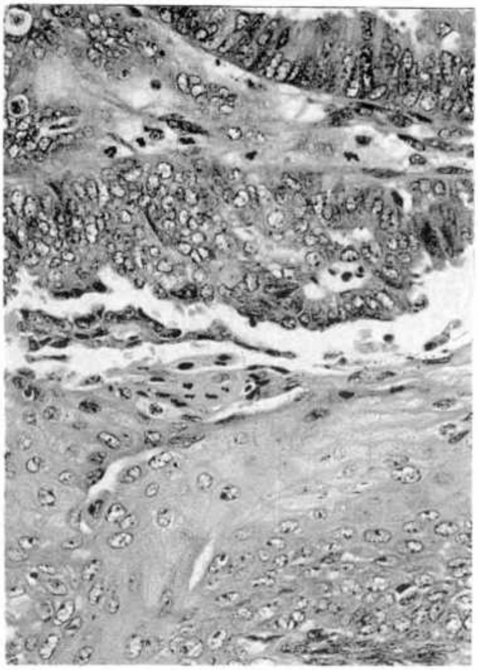


Fig. 1. The endometrial carcinoma showing squamous metaplasia. Haematoxylin and eosin ×184.

extension into the cervix or vagina. However, within the lumen of both fallopian tubes there were detached collections of degenerate squamous cells and keratin, more abundant in the left tube (Fig. 2). The serosa of the uterus, the mesovarium, the mesosalpinx of both sides, and in particular the left, and the surface of the left ovary showed fragments of degenerate squamous cells and keratin surrounded by foreign body giant cells and inflammatory cells (Fig. 3). In addition, occasional intact and apparently viable tumour fragments were identified. These were surrounded by small numbers of mesothelial and inflammatory cells. No tumour was identified within the substance of the ovaries. The lymph node sampled was free of tumour.

The nodule from the pouch of Douglas was partially covered by mesothelium, indicating that it had previously been attached to the peritoneum. It contained fragments of degenerate squamous cells, keratin and numerous foreign body giant cells, with an intense acute inflammatory reaction; the largest fragment measured up to 0·7 mm in size (Fig. 4).

An empirical stain for keratin (Wood & Green 1958) was performed and similar staining reactions were noted with the keratin in the endometrial tumour and in the peritoneal lesions (Fig. 5).

Immunohistochemical staining for cytokeratins was performed using monoclonal antibodies to cytokeratins, CAM 5·2 (Becton Dickinson, CA, USA) and LP 34 (Dakopatts AS, Denmark). Cells of the detached tumour fragments and reactive mesothelial cells were strongly positive with CAM 5·2 (Fig. 6). Both glandular and squamous components of the uterine tumour also stained positively. With LP 34, there was positive staining of squamous cells of the tumour fragments, squamous cells showed positive staining, but glandular cells were negative; a similar pattern was observed in the endometrial tumour with this antibody.

Cytology

Examination of ascitic fluid from the pouch of Douglas showed reactive mesothelial cells and clusters of large cells with a formation suspicious of adenocarcinoma, although a definite diagnosis of malignancy could not be made on this material.

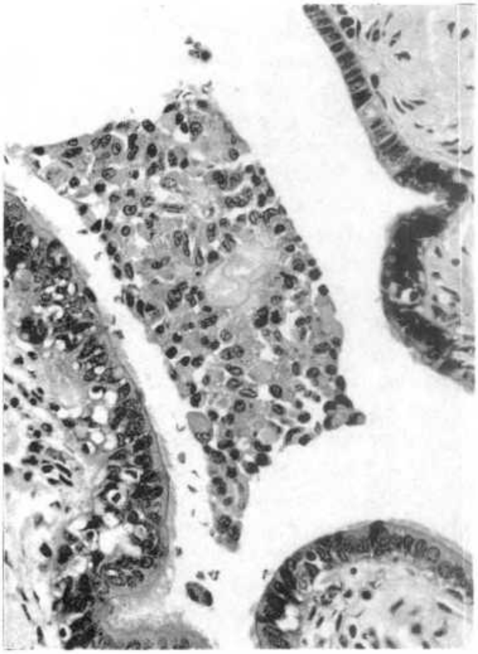
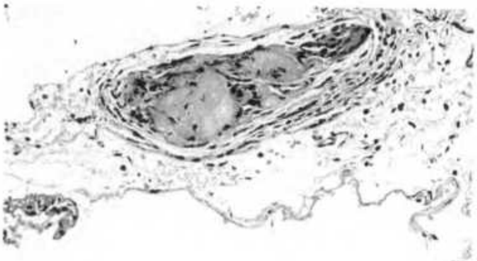


Fig. 2. Fallopian tube containing inflammatory cells and keratinous debris. Haematoxylin and eosin ×184.



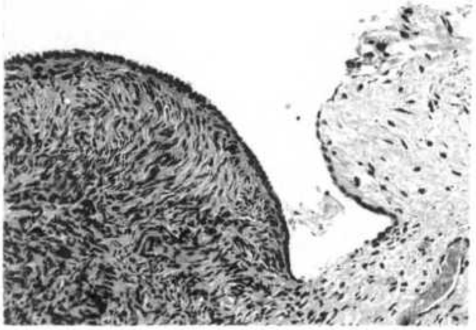


Fig. 3. A foreign body granuloma to keratin on the surface of the ovary. Haematoxylin and eosin ×92.

Discussion

The presence of keratin granulomas in the peritoneal cavity is uncommon and has classically been associated with rupture or slow leakage of keratin and sebaceous material from a cystic teratoma (dermoid cyst) of the ovary (Abitol *et al.* 1959). Chen *et al.* (1978) reported five cases in which peritoneal keratin granulomas were found in patients who had endometrial carcinoma with squamous metaplasia, and Williams *et al.* (1984) reported a similar occurrence in a patient with endometrial adenosquamous carcinoma. The granulomas, forming macroscopic nodules, were observed in the peritoneum overlying the uterus, tubes, broad ligaments, ovaries, sigmoid colon, appendix, and urinary bladder. In our patient the single detached nodule and adhesions of surgery noted showed a florid peritoneal reaction to keratin associated with an acute inflammatory response and free fluid in the pouch of Douglas. The presence of degenerate tumour cells and keratin in the fallopian tubes and the concentration of granulomas around the ovary and mesosalpinx indicates that the keratinous material gains access to the peritoneal cavity through the fallopian tubes. This reflux of tumour tissue through the tube would be similar to that of retrograde menstruation, proposed in the aetiology of some cases of pelvic endometriosis (Sampson 1924).

In addition to keratin granulomas, apparently viable tumour fragments with both malignant glandular and benign squamous elements were present within the peritoneal tissue in our patient. Free fluid aspirated from the pouch of Douglas also contained suspicious cells. Williams *et al.* (1984) found viable tumour cells in the fallopian tube in their patient but not in the peritoneum. Chen *et al.* (1978) did not find tumour cells in the peritoneal lesions of their patients and have emphasized that, in the absence of tumour cells, these lesions should not be interpreted as evidence of metastatic spread. The detached tumour fragments we noted, surrounded by reactive mesothelial and inflammatory cells, were clearly not true metastatic lesions although it is possible that they have the potential for metastatic growth.

There has been considerable controversy in the literature concerning the occurrence of transtubal spread of endometrial carcinoma cells and the role of diagnostic procedures, such as curettage, in facilitating this (Sampson 1924;

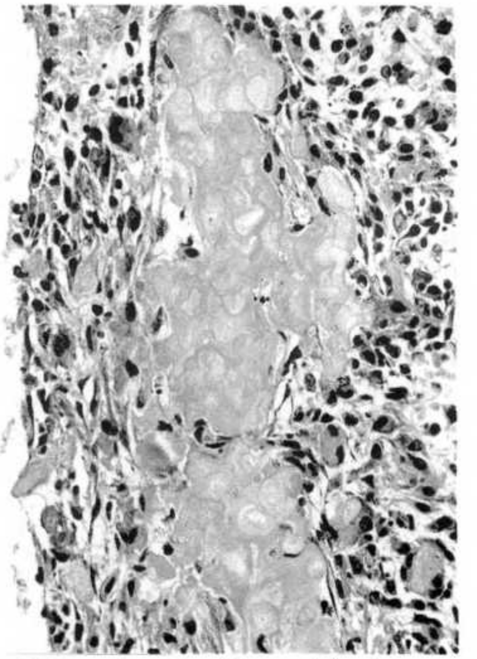


Fig. 4. The peritoneal nodule containing degenerate tumour cells surrounded by inflammatory cells and foreign body giant cells. Haematoxylin and eosin ×184.

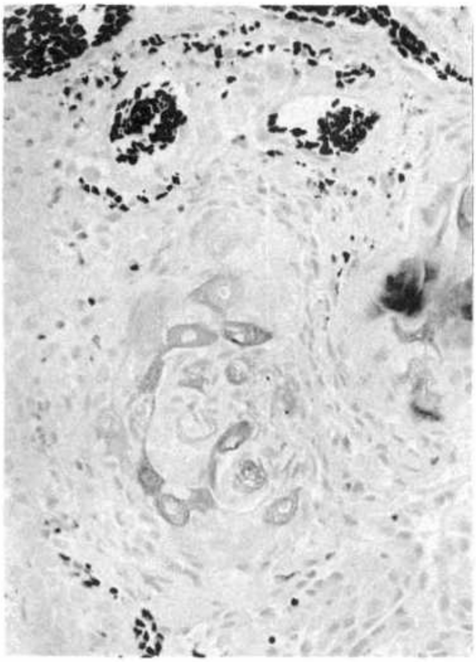


Fig. 5. A peritoneal keratin granuloma stained empirically for keratin. Pontacyl violet counterstained with luxol fast yellow ×184.

Novak 1927; Lynch & Dockerty 1945). Some authors have maintained that tubal transmission of tumour cells is uncommon and that apparent implantation cancers are more likely to be caused by lymphatic dissemination of the tumour cells (Novak 1927; Lynch & Dockerty 1945). Others (Hoeg 1956; Dahle 1956) have concluded from cytological studies of tubal smears and washings, and peritoneal washings, that cells from endometrial carcinoma in a high proportion of patients (60%) may be found in the tubes and that in some of these patients they are also demonstrable in peritoneal washings. Creasman *et al.* (1981) have found positive peritoneal cytology in 8% of patients with carcinoma confined to the endometrium and it is probable that some of these represent direct tubal transmission of tumour cells.

In our patient a diagnostic curettage had been performed several days before the radical hysterectomy. It is possible that the curettage contributed to tumour dissemination, a view supported by the finding of intact tumour fragments in the peritoneum. Escape of tumour tissue at the time of operation, due to manipulation, is unlikely as the tubes were clamped at an early stage of the procedure to prevent this. The patient also had an unsuccessful dilatation and curettage about 18 months earlier, when she first presented with symptoms. It is speculative whether the adhesions found tethering the uterus to the bladder and the rectum on the left side at the time of hysterectomy could have been due to perforation (for which no evidence was found on histological examination), escape of keratinous material through the tube, or unrelated pelvic inflammatory disease. Certainly far more granulomata were found around the uterus and adnexa on that side. However, dissemination of the keratinous material through the tube can occur in the absence of an operative procedure, a fact illustrated by the case reported by Chen *et al.* (1978) where peritoneal keratin granulomas were found in a patient whose curettage was immediately followed by hysterectomy.

Some of the peritoneal keratin globules found in our patient were much larger than the fragments of keratin in the tube and intact tumour fragments in the peritoneum. Williams *et al.* (1984), on the basis of similiar findings, have put forward the hypothesis that a tumour implant might have survived and evolved into a keratinous nodule similar to the phenomenon of maturation seen in some metastatic tumours

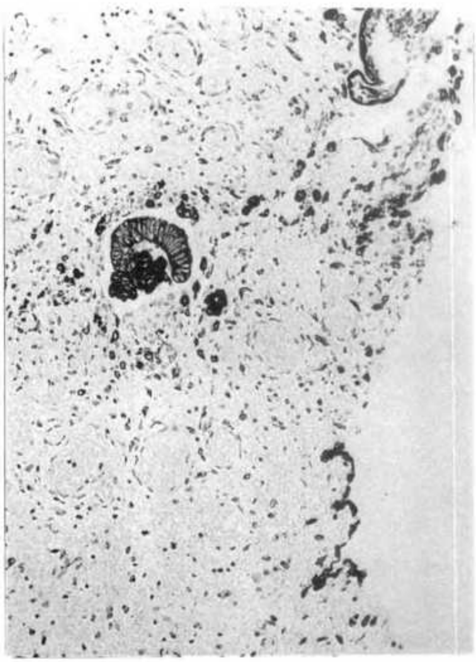


Fig. 6. Immunoperoxidase staining for cytokeratins showing viable tumour fragments in the peritoneum. Note the reactive mesothelial cells. CAM 5·2×92.

such as teratomas and neuroblastomas. Follow-up studies of three patients by Chen *et al.* (1978) have suggested a favourable outcome in patients with peritoneal keratin granulomas from endometrial carcinoma with squamous metaplasia. The prognostic implications when tumour fragments or cells are also present in the peritoneum is less clear, particularly in patients who have otherwise good prognostic features, i.e. well-differentiated carcinomas confined to the endometrium. Several authors have commented on the fact that some low-grade endometrial carcinomas, particularly adenoacanthomas, tend to recur at the vaginal vault, usually after long intervals (Brown *et al.* 1968; Finn 1950; Lederman *et al.* 1987). This has been attributed either to implantation of tumour cells shed through the cervix, or to lymphatic metastases. Another possibility, raised by this case, is that tubally transmitted malignant cells, present in the pouch of Douglas, may be implanted from the peritoneum into the site of vaginal closure.

In conclusion, this report illustrates that granulomatous peritonitis to keratin may be an unusual complication of endometrial carcinomas containing squamous elements. The presence of peritoneal keratin granulomas should alert the pathologist to the possibility of transtubal spread of viable tumour cells into the peritoneal cavity.

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Choriocarcinoma in mother and child. Case report

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Case report

A 30-year-old woman who had had two previous normal pregnancies was admitted in labour at term in her third pregnancy. She had a normal delivery and gave birth to an apparently healthy girl with a birthweight of 3750 g. The placenta looked normal and was not sent for histological examination. Within the first 24 h the infant developed anaemia. This was ascribed to early clamping of the cord, the infant received a blood transfusion and was discharged 7 days later. At 20 days of age the child suddenly died at home. The autopsy revealed a rupture of a greatly enlarged liver. The rupture was caused by a haemorrhagic tumour involving the whole right lobe. The initial microscopic diagnosis was hepatocellular carcinoma. No further tumours were found.

Because the mother had persistent vaginal bleeding she had a dilatation and curettage at 10 weeks after the delivery. The uterus was enlarged to the size of an 8 weeks pregnancy. The curettings consisted of masses of abnormal trophoblastic cells with mitotic activity and without any villous structures (Fig. 1). Thus, the criteria for choriocarcinoma were fulfilled. The same pathologist re-examined the sections of the liver tumour and this was found to be morphologically identical to the choriocarcinoma of the mother (Fig. 2). The mother was referred to the department of obstetrics and gynaecology at the Karolinska Hospital for further assessment and treatment. Pelvic arteriography showed an enlarged uterus without any typical findings of choriocarcinoma. Ultrasound and tomographic examinations of the abdomen were negative. A chest radiograph was normal. However, serum human chorionic gonadotrophin (hCG) was elevated at 24 200 i.u./l (first international standard). Treatment was started with methotrexate/folinic acid, using the regimen developed by Goldstein *et al.* (1978) for non-metastatic disease. The patient received three treatment courses and serum hCG was not detectable after the second course. The patient was allowed to become pregnant again after 1 year free of disease but had an ectopic pregnancy. Six months later she had a miscarriage but shortly after this she conceived again and gave birth to a healthy girl after an uneventful pregnancy 42 months after her disease. The patient has now been free of disease for almost 7 years.

Discussion

Choriocarcinoma is an uncommon disease. In Sweden between two and nine patients are treated yearly (National Board of Health and Welfare, The Cancer Registry, Sweden 1966–1982). We believe the present report of choriocarcinoma in both mother and infant to be the ninth report of this unusual association in the world literature. There are four additional cases where fetal metastases from a placental choriocarcinoma occurred (Table 1). In these no disease was ever found in the mothers. Unless the disease is actually found in the mother the possibility of a primary choriocarcinoma in the child cannot be ruled out. Primary congenital tumours do occur, for example rhabdomyosarcoma and neuroblastoma, but, with choriocarcinoma, we find it more plausible that the primary placental tumour disappears with the expulsion of the placenta. Presumably, as in our patient, some infants with choriocarcinoma are diagnosed incorrectly unless the disease is detected in the mother.

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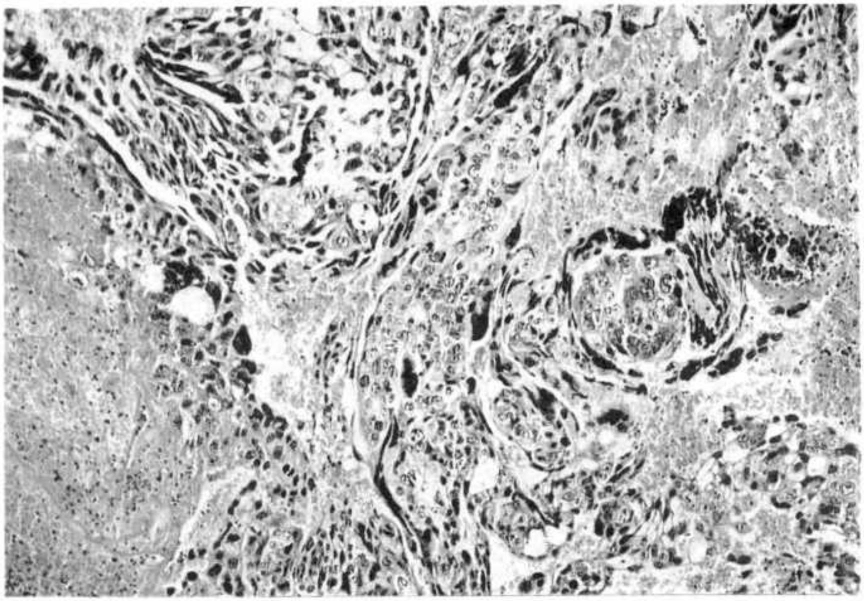

Fig. 1. Choriocarcinoma in curettage from mother (×75).

The clinical features of the 12 infants reported in the world literature are consistent. Seven were female and five were male. First signs of disease were seen within the first 6 months of life and two were stillborn. None lived for longer than 8 months. As in our patient, all the children had severe anaemia and seven had hepatomegaly. In three girls there were signs of hypersecretion of female sex hormones. Pulmonary metastases were seen in 5 of 8 chest radiographs. Three children had cutaneous tumours. In only two of the 12 patients was the disease first observed in the mother. When choriocarcinoma is first diagnosed in a child there should be a careful search for choriocarcinoma in the mother. Even if the initial measurement is

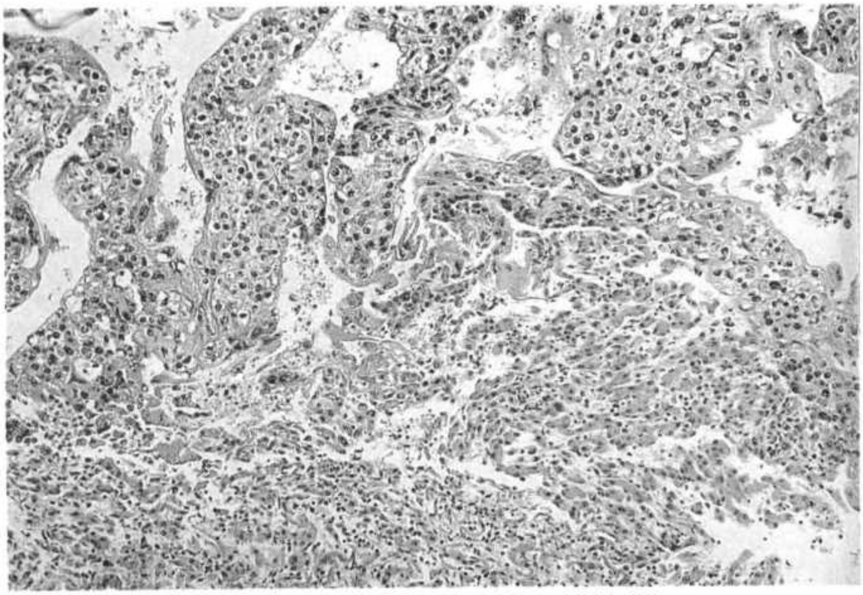

Fig. 2. Metastasis from choriocarcinoma in the liver of the child (×75).

Table 1. Reports of choriocarcinoma in mother and child

		Child			Mother	
Patient no.	Authors	Sex	Age at first sign of disease (weeks)	Age at death (weeks)	hCG	Follow-up postpartum
1	Emery (1952)	M	2	6	−	ND 10 months
2	Kay & Read (1953)	F	21	30	−	ND 11 months
3	Buckell & Owen (1954)	M	6	7	+	ND 18 months
4	Mercer *et al.* (1958)	F	4	30	+	Death 9 months
5	Daamen *et al.* (1961)	F	26	35	+	Death 7 months
6	Witzleben & Bruninga (1968)	F	5·5	7	+	Metastasis 5 months
7	Kelly *et al.* (1971)	M	Birth	13	−	ND 3 years
8	Aozasa *et al.* (1981)	F	8	13	+	Death 6 months
9	Nieuwenhuijzen *et al.* (1977)	F	Stillbirth	Stillbirth	+	ND 6 months
10	Kalifa *et al.* (1981)	M	8	11	−	ND 10 months
11	Tsukamoto *et al.* (1986)	M	Stillbirth	Stillbirth	+	ND 9 months
12	Avril *et al.* (1986)	F	Birth	3·5	+	Metastasis 14 months
13	Present study	F	Birth	3	+	ND 7 years

ND, No disease.

normal, monitoring of the serum hCG should continue for a year since tumours may develop several months after delivery.

Three of the 12 mothers died. Most centres treating tumours of the trophoblast report cure rates approaching 100% in patients with non-metastatic and metastatic low-risk gestational trophoblastic disease (Goldstein *et al.* 1978; Berkowitz *et al.* 1986; DuBeshter *et al.* 1987; Newlands *et al.* 1986; Hammond *et al.* 1980). If, however, the patient becomes sick after term pregnancy and does have a metastasis (which is frequent) she has a poor prognosis. In this group cure rates range from 51% to 84% (Berkowitz *et al.* 1986; DuBeshter *et al.* 1987; Bagshawe 1984; Newlands *et al.* 1986; Surwit & Hammond 1980; Gordon *et al.* 1985; Lurain & Brewer 1985; Hammond *et al.* 1980).

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Ovarian fibromatosis with minor sex cord elements. Case report

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Case report

A 22-year-old nulliparous woman was admitted complaining of intermittent lower abdominal pain and amenorrhoea of 3 months duration. She had had an irregular menstrual cycle with scanty infrequent periods since menarche at the age of 18. Four months prior to admission a combined oestrogen and progesterone pill was prescribed for contraception. One month later she had a heavy withdrawal bleed. She did not restart the pill and remained amenorrhoeic until her admission to hospital.

On examination there was mild tenderness in the right and left iliac fossae. No evidence of virilization was present. On vaginal examination the uterus was of normal size and contour and was in the retroverted position. Firm poorly defined masses were palpated in each lateral fornix. The haemoglobin was 15 g/dl, white cell count $4{\cdot}9\times10^9$/l, and urine culture was negative. A pelvic ultrasound scan did not reveal any significant abnormality. Urine hCG was negative.

At laparotomy both ovaries were enlarged, grey/pink in colour, and tubular in shape with surface projections and had a rubbery consistency. No macroscopically normal tissue was seen in either ovary. The pelvic viscera were otherwise normal. No ascites was present. A bilateral oophorectomy was performed. The patient made an uneventful recovery. When seen 6 weeks later she complained of hot sweats and flushes Hormone replacement therapy was started.

Gross pathology. One ovary measured 14×6×4 cm, the other 9×6×3 cm. Both had smooth external surfaces with sausage-shaped projections measuring up to 10 cm in length and 3 cm in maximum diameter. Sectioning revealed grey-white firm tissue with several small cortical cysts up to 0·8 cm in diameter.

Histology. On histological examination, aggregates of undifferentiated sex cord-type cells were seen in a fibromatous stroma (Fig. 1).

The stromal component was characterized by spindle cells with a storiform and fascicular pattern showing dense pericellular reticulin. There was abundant collagen formation. The nuclei of the stromal cells were elongated and fusiform with occasional prominent nucleoli. No mitotic figures were seen. Atretic follicles were present. No luteinized stromal cell aggregates were seen and there was no oedema. The fibromatous stroma surrounded normal ovarian structures and cortical antral follicles with no displacement of native ovarian structures. A small simple surface serous adenofibroma was also present in one of the ovaries, clearly demarcated from the fibromatous area

The sex cord element consisted of occasional small aggregates of undifferentiated sex cord-type cells with a suggestion of poorly defined tubular structures. Occasional cells were present with well-marked nuclear grooves; these appeared indistinguishable from granulosa cells. Some of the aggregates contained poorly formed apparent Call-Exner bodies. The largest aggregate was 1 mm in greatest dimension. These cells

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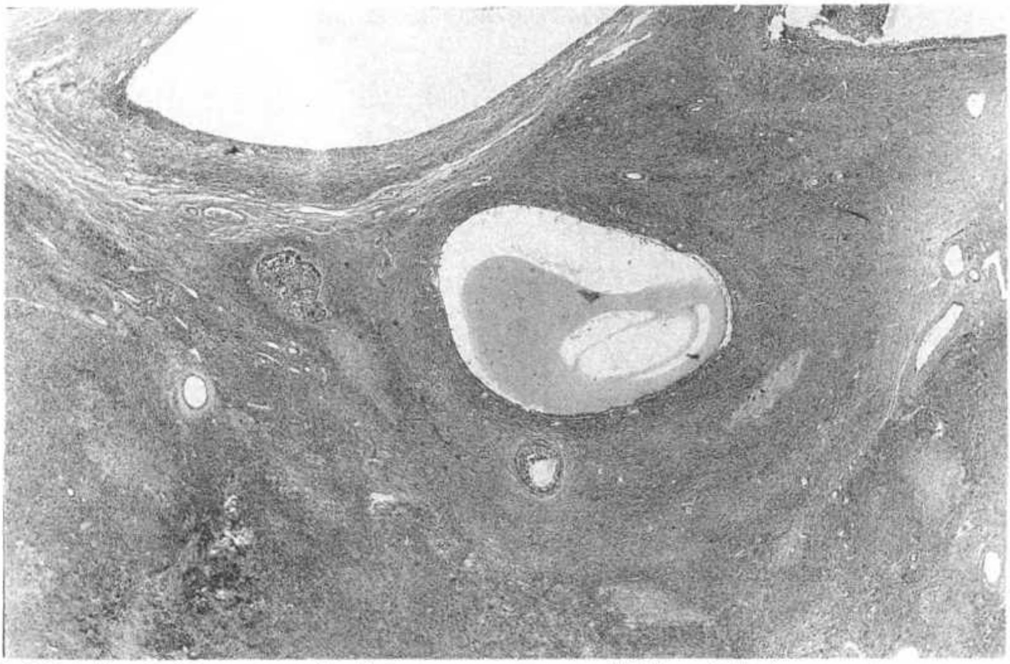

Fig. 1. Spindle-celled tissue surrounding, but not compressing, antral follicles, a follicular cyst, and an aggregate of undifferentiated sex cord-type cells.

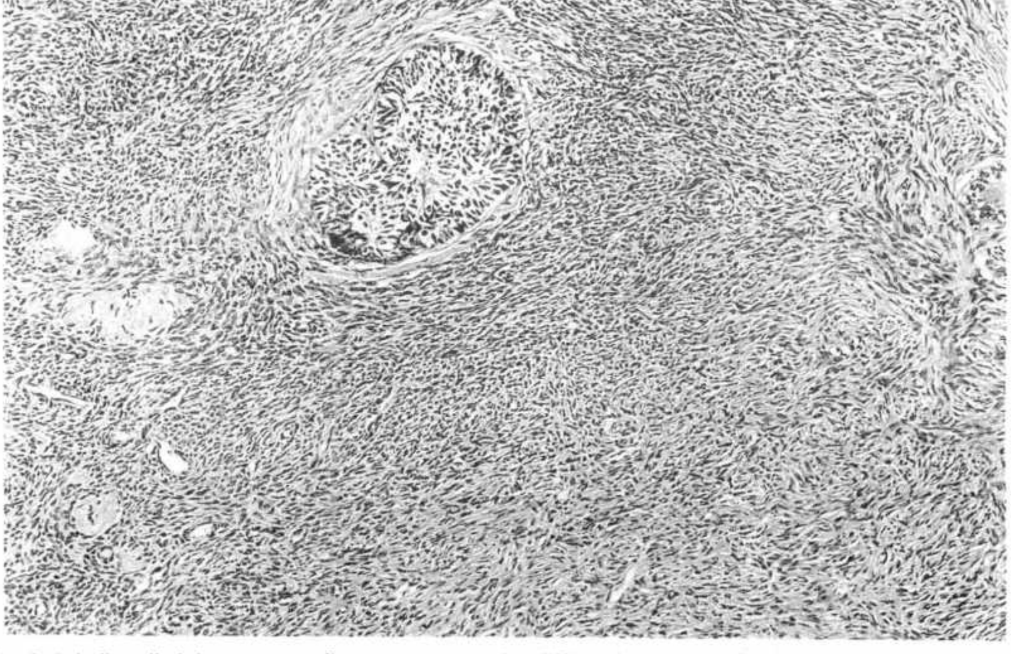

Fig. 2. Spindle-celled tissue surrounding an aggregate of undifferentiated sex cord-type cells.

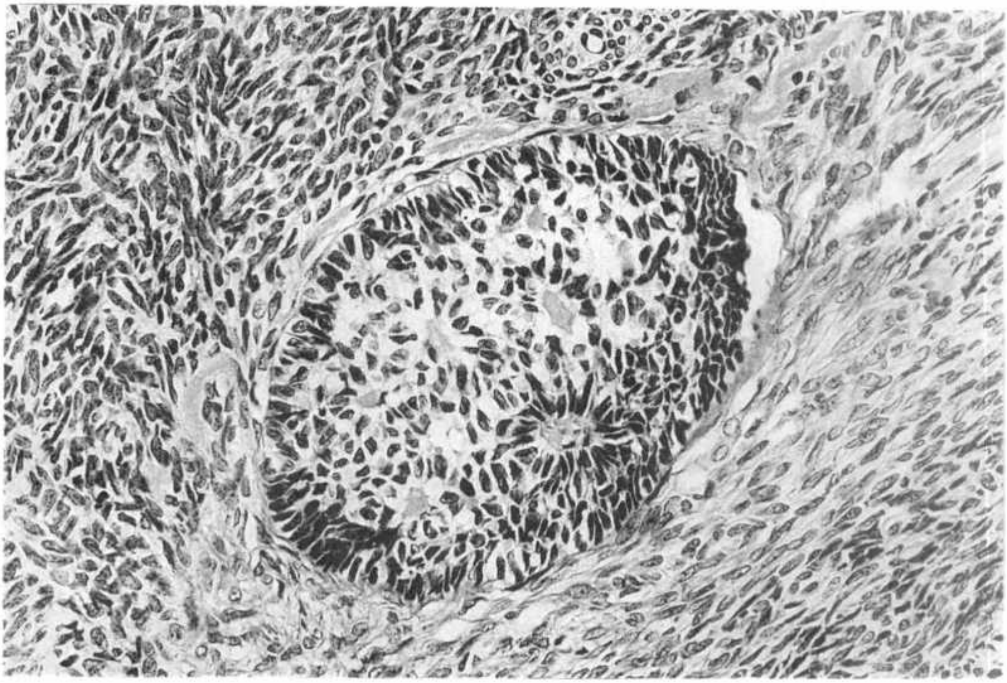

Fig. 3. High-power view of an aggregate of sex cord-type cells showing a suggestion of tubular structure and a poorly formed Call-Exner body surrounded by spindle-celled stroma.

were sharply demarcated from the surrounding stroma (Figs 2 & 3).

Discussion

This lesion was classified as 'ovarian fibromatosis with minor sex cord elements'. Ovarian fibromatosis is an uncommon non-neoplastic condition described by Young & Scully (1984). To date, only 14 cases have been documented in the literature (Young & Scully 1984, 1987). It is a disease of young women characterized by a tumour-like enlargement of one or both ovaries. The average age of the patients in the series of 14 women described by Young & Scully was 25 years (range 13–39). The condition usually presents with menstrual abnormality, amenorrhoea, and rarely virilization. On histological examination there is proliferation of fibroblasts with a production of abundant collagen which surrounds rather than displaces residual ovarian structures.

Ovarian fibromatosis must be distinguished from two similar conditions: ovarian fibromas and massive ovarian oedema. Ovarian fibromas are more common in middle age (Dockerty & Masson 1944; Morrison & Woodruff 1964) and are characterized by discrete fibrous nodules in the ovarian stroma which displace rather than surround ovarian structures. Massive ovarian oedema (Kalstone *et al.* 1969) is similar to ovarian fibromatosis in that residual normal ovarian structures are present surrounded by an oedematous stroma.

It has been postulated that the similar age range and clinical manifestation of ovarian fibromatosis and massive ovarian oedema, and the similarity in their histological features strongly suggest that both conditions are closely related and may represent differing morphological expressions of the same disorder (Young & Scully 1984).

The presence of sex cord stromal elements in the fibromatous ovaries may be a chance association of neoplastic and non-neoplastic conditions. Alternatively, both conditions may be of common aetiology suggesting that fibromatosis is a neoplastic rather than a non-neoplastic proliferation of ovarian stroma.

Our patient is particularly unusual because of the presence of small aggregates of granulosa cells with probable Call-Exner bodies. Young & Scully (1983) reported a series of seven ovarian fibromas with small nests or tubules composed of cells resembling granulosa cells, Sertoli cells, or indifferent cells of sex cord type. These tumours were classified as 'fibromas with minor sex cord elements'. In their series of 14 cases of ovarian fibromatosis, Young & Scully (1984) reported a proliferation of cells of sex cord type in three cases: Call-Exner bodies were present in one case. To the best of our knowledge, this is the only case of ovarian fibromatosis with minor sex cord elements reported in the British literature.

The non-neoplastic nature of ovarian fibromatosis taken in association with the young age at which it occurs has important therapeutic implications. Wedge resection of the ovary has been shown to be adequate therapy. In the series described by Young & Scully (1984), one woman subsequently became pregnant on two occasions following wedge resection for bilateral ovarian fibromatosis. However, when confronted with bilateral ovarian tumours at the time of surgery, it is impossible to be certain whether or not one is dealing with malignancy. Although bilateral wedge resection or unilateral oophorectomy with biopsy of the other ovary may be considered, the danger of disseminating neoplastic cells must always be considered. In retrospect, this case could have been managed more conservatively, but at laparotomy both ovaries were completely abnormal in appearance with the risk of malignancy present. We would suggest that frozen section examination of ovarian wedges may have a place when fibromatosis appears to be a possibility.

Because of its rarity, it is not possible to be dogmatic regarding the prognosis for this case. However, like fibromatosis of the ovary (Young & Scully 1984), it is likely to behave in a benign fashion and the outcome is unlikely to be modified by the minor granulosa cell component.

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SHORT COMMUNICATIONS

Alternative vacuum supplies for ventouse deliveries

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Assisted deliveries using the ventouse have never been as popular in the UK as in certain other countries. This has been put down to inadequate training, poorly maintained equipment, poor choice of patients and the innate conservatism of many doctors. There is little doubt, however, that the right equipment in the right hands can achieve impressive and safe results (Bird 1982).

For some years dedicated electric vacuum pumps have been available. At a cost of around £1500 these appear more effective in several respects than the familiar hand pump, but may be considered a luxury in the current economic climate.

Simple alternatives to dedicated pumps, that cost nothing, and are available in virtually all delivery rooms are the hospital central piped vacuum system and/or portable suction machines designed for anaesthetic or theatre purposes. We investigated the suitability of these cheap, simple, but apparently unpublicized vacuum sources.

Method

To achieve the degree of vacuum needed for oropharyngeal suction, etc. using hospital vacuum supplies, plug-in reducing and controlling valves are available. A typical version is finely controllable between 0 and −760 mmHg (0 and −1 bar) of vacuum and has a quick-release on/off lever. Portable suction machines achieve a similar vacuum. This is, of course, the same range achievable with dedicated hand and electric devices.

The ventouse cup, in our case silicone rubber, was attached directly to the bottle built into the vacuum devices, and a normal ventouse delivery proceeded to. In this trial the vacuum was raised quickly from −0·2 to −0·8 bar after carefully checking the application of the cup.

To assess their ease of use and practicality, 10 deliveries were performed using each of these sources. All deliveries were performed by the authors.

Results

Ten consecutive ventouse deliveries were performed using the hospital piped vacuum as a vacuum source. No problems were experienced. Three deliveries were from the occipito-posterior, two from the occipito-transverse and the remaining five from the occipito-anterior position, eight being delivered from the mid-cavity. Fetal weights ranged from 2040 to 3760 g (mean 3270, SD 370 g). The vacuum achieved was −600 mmHg in six cases, −580 mmHg in three cases, whilst in one case only −510 mmHg could be developed, but this last delivery proceeded uneventfully at this vacuum. No fetal morbidity was noted.

Ten further consecutive ventouse deliveries were performed using portable anaesthetic/theatre suction pumps as a vacuum source. No problems were experienced. Two deliveries were from the occipito-posterior, five from the occipito-transverse and the remaining three from the occipito-anterior position, all being delivered from the mid-cavity. Fetal weights ranged from 2525 to 4300 g (mean 3368, SD 577 g). The vacuum achieved was −600 mmHg in all cases. No fetal morbidity was noted.

Discussion

When referring to ventouse deliveries, published papers and textbooks recommend the use of a dedicated hand or electric pump (Chalmers 1971). Except in primitive surroundings the use of an automatic pump has much to recommend it, not least its ability to maintain a set vacuum in the face of intermittent slight leakages from the system or cup.

Dedicated electric pumps may not, however, be considered cost effective in a unit performing few vacuum extractions, or where senior colleagues lack experience in their use. Personnel using old or badly maintained hand devices may fail more frequently, and consequently inbuilt prejudices may be strengthened.

We have demonstrated that the required vacuum can be developed easily, smoothly and accurately by either of the methods outlined above, and satisfactory deliveries proceeded to, using sources already available on most labour wards.

Hospital vacuum devices are calibrated in a confusing variety of units (although most cover equivalent ranges), and it is necessary to realize this when contemplating alternative uses. The accepted ventouse vacuum of $0{\cdot}8\ \mathrm{kg/cm^2} \simeq 600\ \mathrm{mmHg} \simeq 0{\cdot}8\ \mathrm{bar} \simeq 80\ \mathrm{kPa}$.

Whilst silicone rubber cups were used in this trial, we have also used Bird cups, and there is no reason why these methods should not be equally effective with Malmstrom cups.

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Tuberculous peritonitis in pregnancy. A follow-up

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We previously reported a very unusual presentation of tuberculous peritonitis in pregnancy (Brooks & Stirrat 1986) in which a 25-year-old multiparous West Indian woman developed septic shock at 33 weeks gestation. A live infant was born by classical caesarean section, this route being necessary because of the extensive inflammatory reaction throughout the abdominal cavity. Access to the lower uterine segment was impossible.

The baby thrived but the mother had a stormy postoperative course, ultimately doing well. Two months after delivery, pelvic examination revealed an involuted uterus fixed to a non-specific mass rising out of the pelvis. She was told that she was 'probably now sterile' but a barrier form of contraception was advised.

Imagine our surprise when in May 1987 she attended the antenatal clinic already about 20 weeks pregnant. She could not recall being told she might be sterile and no contraception had been used. Her dates were uncertain but were confirmed by ultrasound.

The pregnancy proceeded uneventfully although there was ultrasound evidence of slight intrauterine growth retardation. She was delivered at 38 weeks gestation by elective caesarean section. Apart from the adherence of a loop of bowel to the anterior abdominal wall, there was no evidence of intra-abdominal pathology. The fallopian tubes were entirely normal and the line of the previous classical caesarean section was hardly noticeable. The lower segment was easily accessible and delivery was effected through it. A live male infant was born weighing 2490 g. Bilateral tubal ligation had been requested and was carried out. Both mother and baby did well. The obstetricians had learned yet another lesson.

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CORRESPONDENCE

Gonococcal and chlamydial antibodies in ectopic and intrauterine pregnancy

Dear Sir,
A recent paper by Robertson *et al.* [*Br J Obstet Gynaecol* (1988) **95**, 711–716] documents the high prevalence of chlamydial antibodies in women with ectopic pregnancy. Gynaecologists also encounter the late effects of chlamydial infection in patients with tubal infertility (Westrom 1975) and in those with chronic pelvic sepsis requiring surgical management.

What can gynaecologists be expected to do to prevent these consequences of chlamydial infection? Firstly, they could assist their colleagues in genitourinary medicine in the difficult task of controlling sexually transmitted infections. Studies have shown that substantial numbers of patients attending for family planning, termination of pregnancy and colposcopy have chlamydial infection. An argument can be made for excluding chlamydial infection in all potential recipients of the intrauterine contraceptive device before insertion. Gynaecologists could have a higher index of suspicion of chlamydial infection in their patients, and be less easily satisfied with the high vaginal swab as a diagnostic test for genital infection.

Most importantly, they could reconsider the management of acute pelvic inflammatory disease. In this condition, the fallopian tubes are being damaged by infection, which, in Europe, is usually chlamydial in nature (Mardh 1980). Correct antibiotic therapy (using an adequate course of an antichlamydial agent), together with treatment of the consort are mandatory. This may be achieved best by collaboration with the local specialist in genitourinary medicine, as already occurs at some centres.

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Authors' reply

Dear Sir,
Thank you for giving us the opportunity to reply to the letter from Dr Coker and colleagues. We agree that the priority must be the effective diagnosis and treatment of chlamydial infections before the onset of tubal damage and its sequelae. Gynaecologists should undoubtedly support the work of their colleagues in genitourinary medicine.

In practice, chlamydial infections, even in the upper female genital tract, are frequently asymptomatic, necessitating laboratory tests. In our view the provision of a high quality laboratory diagnostic service for chlamydial infections should be a major priority of both gynaecology and genitourinary medicine. All too often such a service is not available or is inadequate. By contrast the Soviet Government has recently initiated the manufacture under licence in the Soviet Union of one of the new generation American kits for chlamydial antigen detection. These kits, with associated spectrophotometers, are being distributed to some 250 different laboratories.

Prevention is better than expensive surgery or in-vitro fertilization to circumvent the late effects of chlamydial infection. Gynaecologists, genitourinary physicians and microbiologists in partnership have to educate health financers in the major problem of chlamydial infections. Moreover, given the difficulties of quality control of tissue culture procedures for chlamydial culture, further research is necessary into alternative methods of diagnosing chlamydial infections in the asymptomatic woman. This is increasingly important given the recent recognition that gamma interferon or neutralizing antibodies may interfere with chlamydial isolation (Byrne & Kreuger 1983; Brunham *et al.* 1983). Alternative approaches include improved antigen detection assays, DNA hybridization using the chlamydial plasmid (Hyppia *et al.* 1985) and the detection of short-term antibodies of the mucosal immune system using improved chlamydial antigens.

Finally, we were puzzled to find that in ectopic pregnancy (Robertson *et al.* 1988) both gonococci and chlamydiae were important whereas in our previous study of infertility with tubal occlusion, gonococci were of little importance (Robertson *et al.* 1987). We suggested this might reflect differences in tubal pathology with these two organisms. Does anyone have any alternative explanations?

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Occult biochemical pregnancy: fact or fiction?

Dear Sir,

The interesting article by Walker and colleagues [*Br J Obstet Gynaecol* (1988) **95,** 659–663] raises the question about the true incidence of early pregnancy loss. In their study the authors did not find any early miscarriages among 38 women, who were attempting to conceive, during 75 menstrual cycles. They concluded that biochemical pregnancies are rather uncommon. In a recent similar study from America, Wilcox *et al.* (1988) estimated the incidence of occult biochemical pregnancies to be 22% (95% CI 16 to 28%) in 707 menstrual cycles. The large discrepancy in estimates between the two studies deserves some comments.

Regarding the methods, the latter study used a highly sensitive and specific radioimmunoassay which reacts with the unique carboxy-terminal region of the beta chain on the human chorionic hormone (hCG) (Armstrong *et al.* 1984). Since this assay measures hCG with no cross-reaction with human luteinizing hormone (hLH) (Wehmann *et al.* 1981), the presence of hLH in the specimens can not explain the difference.

The difference in recruitment of subjects could have introduced some bias, but this is unlikely. On the other hand, Walker *et al.* (1988) also had a subsample of 16 women who had had a previous episode of first trimester miscarriage which could bias the results away from the null value (Kleinbaum *et al.* 1986).

It is, however, a more plausible explanation that perhaps there actually did occur some early losses among the subjects, but that these were missed because of the lower sensitivity and specificity of the assays used. If one biochemical pregnancy did arise in the study (1 loss out of 26 pregnancies), the point estimate would have been 4%, and the corresponding 95% CI 0 to 11% (Kleinbaum *et al.* 1986). The study by

Wilcox *et al.* (1988) also gives more precise estimates because of the larger sample size.

On this background some of the conclusions in the article by Walker *et al.* (1988) need to be reassessed in light of the larger and more valid and epidemiologically appropriate study by Wilcox *et al.* (1988).

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Authors' reply

Dear Sir,

As Dr Brattebø correctly points out, a much larger study than ours, using a more sensitive yet apparently highly specific assay for hCG has provided evidence that early losses of clinically unrecognized pregnancies do occur in the normally fertile population. At issue is the frequency of such losses and how they are identified.

Our study showed unequivocally that late luteal phase rises in hCG, identified using the NIH SB6 antiserum as in the first reports (Miller *et al.* 1980; Edmonds *et al.* 1982), do not provide adequate evidence for the recognition of unsuspected trophoblast activity. Therefore, previously reported high incidences of biochemical pregnancies were probably substantially overestimated. Dr Brattebø quotes from the paper by Wilcox *et al.* (1988) the figure of 22% occult biochemical pregnancies in 707 cycles. However, this figure of 22% relates the number of early pregnancy losses (43) to the total number of pregnancies (subclinical and clinical), 198. It is more meaningful to express early losses in terms of the total number of cycles without a clinical pregnancy, i.e. 43 early losses out of 552 cycles (7·8%). It should also be pointed out that many of these 43 events were not truly subclinical because, as Wilcox *et al.* (1988) state in their discussion, they were not distinguishable from the earliest clinically recognized miscarriages. Only seven occurred by day 28 of the cycle and only 13 by day 30. It is important, therefore, to define what is meant by the term 'biochemical pregnancy' and to distinguish it from early clinical miscarriage. Defining an occult biochemical pregnancy as a very early pregnancy, recognized only by biochemical means, and lost at the time of expected menstruation, the data of Wilcox *et al.* (1988) would suggest that a biochemical pregnancy occurs in 1–2% of normal menstrual cycles. In our much smaller series, menstruation occurred in all 50 non-conception ovulatory cycles at the expected time without any biochemical evidence of pregnancy.

It is important to recognize that early pregnancy losses were identified by Wilcox *et al.* (1988) when hCG excretion exceeded an arbitrary limit for an arbitrary period of time. Because of the extreme sensitivity of their assay, hCG excretion is detected in non-pregnant women and healthy men. It is possible that their criteria for trophoblast activity are too generous and may have overdiagnosed biochemical pregnancy. A more rigorous approach would have been to subject the data to mathematical pulse detection analysis.

Finally we would reiterate that based on our relatively small sample we did not claim that biochemical pregnancies do not occur, only that previously quoted incidences were gross overestimates and the data published by Wilcox *et al.* (1988) are consistent with that view.

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Retrieval of intrauterine contraceptive devices with missing tails, using Lamicel

Dear Sir,

In a recent issue of your Journal Drs Johnson & Moodley [*Br J Obstet Gynaecol* (1988) **95**, 97–100] advocated the use of Lamicel to facilitate retrieval of intrauterine contraceptive devices (IUCD) with 'missing' tails. Their paper was colourfully written, describing a method used in a hospital with the majority of patients being Zulu-speaking Africans. Instrumental removal of the IUCD after Lamicel dilatation of the cervix was successful in 30 out of 31 women with 'missing' threads.

A more simple and equally effective method to be used in patients with 'missing' IUCD threads, in whom pregnancy is excluded, is to retrieve retracted IUCD threads by means of a disposable thread retriever (Retrievette). In clinical studies (Åkerlund *et al.* 1982; Pap de Pesteny *et al.* 1986) it was found that this instrument can be used in women with retracted threads at a normal gynaecological investigation without anaesthesia. The retracted threads can almost invariably be retrieved with minimal discomfort. Only in cases where threads have been cut too short at the IUCD insertion, or the device is malpositioned so that the threads can not reach into the vagina, do more complicated and painful procedures have to be undertaken. In fact, after thread retrieval the IUCD can be left *in situ* in women who so wish.

This instrument is now available in the UK (Thames Laboratories, Lower Square, Old Isleworth, Middlesex TW7 6RL), Mainland Europe (Laboratoire CCD, 44, rue Notre-Dame de Lorette, Paris) and Scandinavia (Dartec AB, Box 117, S-23010 Skanör, Sweden).

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Uteroplacental and umbilical artery blood velocity waveforms in placental abruption assessed by Doppler ultrasound

Dear Sir,

We have read with great interest the case report by Morrow & Knox Ritchie on flow measurements in placental abruption [*Br J Obstet Gynaecol* (1988) **95**, 723–724]. We have had an opportunity to perform duplex-Doppler flow measurements in one patient with partial and in another with complete placental abruption, and our findings concur with those of the authors.

Our first patient was a 28-year-old primigravida who was treated with betamethasone and fenoterol at 32 weeks gestation for vaginal bleeding and uterine contractions; she was then referred to our department. She was anaemic (haematocrit 28%) and the external cardiotocograph recording (CTG) showed type II dips. Over the next 48 h the CTG deteriorated (tachycardia 180–200 beats/min with loss of beat-to-beat variation and intermittent decelerations) and her temperature rose to 37·8°C. Ultrasound showed a growth-retarded fetus presenting by the breech. The placenta was dorsal and fundal, but no signs of placental separation were seen. Flow measurements (Table 1) showed a borderline A/B ratio in the fetal descending aorta. The tentative diagnosis was intrauterine infection and she was delivered by caesarean section. The female baby weighed 1600 g and had Apgar scores of 1 and 5 at 1 and 5 min, respectively; the umbilical artery pH was 7·20 and intrauterine sepsis was not confirmed. The placenta weighed 435 g and there was a retroplacental clot weighing 200 g.

Our second patient was 25 years of age. Her first pregnancy had been complicated by pre-eclampsia, preterm birth and neonatal death due to respiratory distress. In the present, second pregnancy she was closely observed for hyper-

Table 1. Flow measurements in the fetal aorta and umbilical artery

		Patient 2 (weeks gestation)				
Blood flow indices*	Patient 1	28	29	30	31	At abruption (31 weeks)
Descending aorta						
A/B ratio	6	4	3	3·5	4·5	∞
PI	3·18	2	2·2	2·0	2·8	4·44
RI	0·83	0 75	0·69	0·71	0·78	1·0
Umbilical artery						
A/B ratio	4·3	4·4	3·4	2·8	2·75	∞
PI	2·5	1·9	2·13	1·5	1·4	1·5
RI	0·77	0·77	0·71	0·64	0·64	1·0

* A/B ratio = peak systolic/end diastolic ratio; PI = pulsatility index; RI = resistance index

tension (up to 160/100 mmHg) and stayed in hospital after 28 weeks gestation. She had no significant proteinuria; twice-daily CTG recordings were normal and blood flow values were in the upper end of the normal range (Table 1). At 31 weeks, the house officer performing the routine CTG at 17.00 hours noted a total loss of beat-to-beat variability and immediately performed a flow measurement, which showed an end-diastolic block in both the fetal aorta and umbilical artery. During this examination a uterine spasm became clinically obvious and placental abruption with a huge retroplacental clot was seen. The patient was immediately transferred to the theatre, but because the fetus was now dead she was not delivered by caesarean section. After 5 h of spontaneous labour a female baby weighing 1470 g (10–25th centile) was stillborn. Delivery of the placenta (440 g) was immediately followed by expulsion of a clot weighing 1800 g.

Our findings in these two patients support the conclusions drawn by Morrow & Knox Ritchie that vascular resistance increases in the fetus when there is marked placental abruption. However, flow measurements are not specific, and clinical signs must establish the diagnosis in this situation. In the rare instance that one is confronted with a placental abruption and a live fetus, priority should be given to fetal rescue rather than to obtaining a flow measurement.

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Morrow, R. J. & Knox Richie, J W (1988) Uteroplacental and umbilical artery blood flow velocity waveform in placental abruption assessed by Doppler ultrasound Case report. *Br J Obstet Gynaecol* **95**, 723-724.

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BOOK REVIEWS

Fetal Echocardiography: An Atlas by Kathryn L. Reed, Caroline F. Anerson & Lewis Shenker. Alan R. Liss, Inc., New York, 146 pages with figures and tables, £62.50

This book is essentially about cardiology but written by obstetricians. It is presented in an extremely simple style. This is not without its merits but it is so oversimplified that it is often inaccurate. The author regurgitates many clichés of received wisdom on fetal cardiovascular physiology which recent observations in the human fetus do not support.

Some of the illustrations are attractive and normal cardiac views are reasonably well covered. Abnormal anatomy is not presented in any logical sequence and the experience of this topic appears very limited. The book is heavily illustrated with drawings which I understand are popular, although I personally do not like them. They do make the book expensive for so little text.

Lindsey D. Allen

Books received some of which may be reviewed at a later date

Clinical Practice in Sexually Transmissible Diseases Second edition by D. H. H. Robertson, A. McMillan & H. Young. Churchill Livingstone, Edinburgh, 1988, 520 pages, 62 illustrations, £49.50

Reproduction, Obstetrics and Gynaecology edited by M. G. Elder. Heinemann Medical Books, Oxford, 1988, 333 pages with figures and tables, £20.00

Hysterosalpingography and Pelvic Ultrasound: Imaging in Infertility and Gynecology by Isabel C. Yoder. Little, Brown & Company, Boston, Toronto, 1988, 220 pages, 152 illustrations, £52.50

Progress in Obstetrics and Gynaecology Volume 7 edited by John Studd. Churchill Livingstone, Edinburgh, 1988, 412 pages with figures and tables, £19.95

Transplacental Effects on Fetal Health (Progress in Clinical and Biological Research Volume 281) edited by Dante G. Scarpelli & George Migaki. Alan R. Liss, Inc., New York, 1988, 376 pages with figures and tables, $70.00

Bronchopulmonary Dysplasia (Volume 4 Contemporary Issues in Fetal and Neonatal Medicine) edited by T. Allen Merritt, William H. Northway Jr & Bruce R. Boynton. Blackwell Scientific Publications, Boston, Oxford, 1988, 452 pages with figures and tables, £45.00

Cancer of the Breast Third edition edited by William L. Donegan & John S. Spratt. W. B. Saunders Company, Philadelphia, London, 1988, 796 pages with figures and tables, £62.00

Diagnostic Cytopatopathology: A Text and Colour Atlas by Chandra Grubb. Churchill Livingstone, Edinburgh, 1988, 224 pages, 640 illustrations, £29.50

Childbirth Education: Practice, Research and Theory edited by Francine H. Nichols & Sharron Smith Humenick. W. B. Saunders Company, Philadelphia, London, 1988, 586 pages with figures and tables, £21.95

Obstetric Ultrasonography and Gynecologic Oncology (Contemporary Issues in Obstetrics and Gynecology Volume 3) edited by R. L. Berkowitz, C. J. Cohen & N. G. Kase. Churchill Livingstone, New York, Edinburgh, 1988, 256 pages, 110 illustrations, £30.00

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COMMENTARY

Does treatment with progesterone prevent miscarriage?

Patients with recurrent or habitual miscarriage are understandably anxious for any worthwhile treatment, and progesterone or its analogues have been and are still widely used but there are a number of unresolved problems.

(1) What is the actual risk of another miscarriage if no treatment is offered?

(2) What proportion of patients can be shown to have a hormone deficiency either in the corpus luteum or the placenta?

(3) If there is evidence of hormone deficiency, is that the cause or the consequence of the miscarriage and does specific treatment have any effect?

(4) Does psychological support prevent some patients from miscarrying again?

The calculated risk of another miscarriage after three miscarriages has been put as high as 73% or even 84% (Malpas 1938; Eastman 1946). The observed frequency is over 50% (MacNaughton 1964; Parazzini 1988) but with any of a wide variety of different lines of treatment the miscarriage rate falls to 20% (Swyer & Daley 1953; Tupper & Weil 1962; Graves 1987).

Among women with recurrent miscarriage selected for endocrine problems, Jones (1976) showed that the corpus luteum was defective in progesterone production between pregnancies in 35%, as judged by endometrial biopsy. More recently Daya *et al.* (1988) reported luteal phase defects in 40% of women with recurrent miscarriage who were assessed by endometrial biopsy and serum progesterone. Logically, if it is to be effective, treatment with progesterone in such patients should be started before implantation.

In early pregnancy removal of the corpus luteum before the end of the seventh week of amenorrhoea leads to miscarriage which can be prevented by progesterone therapy but not by oestrogen (Csapo *et al.* 1972, 1973). On that evidence progesterone is indispensable for the maintenance of early pregnancy.

Further interest has been added to the argument about the clinical significance of progesterone deficiency in miscarriage with the discovery that mefipristone, an anti-progesterone, can effectively terminate early pregnancy up to 41 days of amenorrhoea (Baulieu 1988). Medical termination with mefipristone and prostaglandin (gemeprost) up to 56 days amenorrhoea is already an acceptable procedure (Urquhart & Templeton 1988).

Between 10 and 25% of normal pregnant patients show some evidence of hormone deficiency during the first or second trimester, and that figure rises to 70% in patients with previous recurrent miscarriage (Macdonald *et al.* 1972). However, in a series of 74 women with recurrent miscarriage, Klopper & MacNaughton (1965) found that up to 10 weeks gestation there was no difference in the pregnanediol excretion curves between the women who later miscarried and those who had a successful pregnancy, and the early pregnanediol output could not be used as an indication for therapy in any one woman. Indeed oestriol excretion was a better indicator, being lower in patients who did eventually miscarry. Their conclusion was that the reduction in hormone production was the effect rather than the cause of the miscarriage and that at the time of reduced pregnanediol excretion the pregnancy was already beyond salvage. The best randomized trials (Shearman & Garrett 1963; Goldzieher 1964; Klopper & MacNaughton 1965; Reijnders *et al.* 1988) have all shown hormone treatment to be no more effective than a placebo and they have in the end advised against active therapy.

If individual randomized controlled trials contain an insufficient number of patients for the result to be statistically significant, a meta-analysis or overview assessment of a collected series of similar reported trials may allow the observer to reach a valid conclusion that would otherwise be missed (Bulpitt 1988). There are problems in the selection of the published reports to be assessed, and of course if the quality of the original material is poor, the reliability of the result will be diluted.

In this issue of the journal (p. 265) Goldstein *et al.* (1989) provide a meta-analysis of randomized controlled trials of progestational agents in pregnancy to assess whether the use of such agents helps to achieve a normal outcome in 'high-risk' pregnancy, as defined by a previous miscarriage, a previous unexplained stillbirth or preterm labour in that pregnancy. Fifteen of 20 trials had combinable data, and Goldstein *et al.* came to a clear conclusion that 'progesterone and its analogues are ineffective in the maintenance of pregnancy'. One of the problems of such wide-ranging meta-analyses is the risk of mixing apples and oranges with an occasional lemon, in this case previous miscarriage, preterm labour and unexplained stillbirth. For example it seems unrealistic to suggest that progesterone inhibition of uterine activity might prevent unexplained stillbirth. However, the authors demonstrate a very thorough selection and assessment of the chosen studies and they suggest that if further trials are to be undertaken they should include only women who have demonstrable hormonal abnormalities and have ultrasound evidence of a live fetus.

By contrast, in another article in this issue (p. 275), Daya (1989) presents a meta-analysis of controlled trials on the efficacy of progesterone support for pregnancy in women with habitual miscarriage. He selected women with habitual miscarriage described in just three suitable reports and identified a total of 50 treated patients and 45 control patients. His conclusion was that while none of these three reported trials showed a beneficial effect, analysis of the combined data indicated a distinct benefit from progesterone therapy. Here too there are qualifications: in the study by LeVine (1964) patients were allocated alternately not randomly; in the study by Goldzieher (1964) not all patients started treatment during the first trimester; and in the series described by Swyer & Daley (1953) the treated patients were given a progesterone implant while some control patients were offered a placebo tablet, and so treatment was not 'blind'. Moreover, as Goldstein *et al.* (1989) point out, none of the studies assessed by Daya included evidence of progesterone deficiency before treatment.

Daya does not appear to be wholly convinced by his own figures and he suggests that while the treatment looks promising, further studies are required. Fortunately both analyses agree on the need for any future trials to be prospective, double blind and randomized.

If statisticians do not agree or do not give a clear message, we need to fall back on clinical judgement and common sense until further information is available. If hormone therapy is ineffective that does not imply that nothing can be done. Many different regimens for treating women with recurrent miscarriage, including immunotherapy, psychotherapy, hormones and vitamins, have all proved successful in about 80% of patients (Swyer & Daley 1953; Rock & Zacur 1983; Graves 1987; Sargent *et al.* 1988). The common factor was described by Javert (1957) as 'tender loving care' and it is interesting to speculate in what way benefit might be mediated through the pregnant woman by positive encouragement instead of negative fatalism.

The development and widespread use of ultrasound scans which can demonstrate a live fetus at 6 to 8 weeks has dramatically changed and narrowed the problem. In their prospective study of patients with an increased risk of miscarriage, Reijnders *et al.* (1988) reported a miscarriage rate of just 4·7% in women who had a live fetus demonstrated on ultrasound scan at 6 weeks. McFadyen (1985) found a rate of miscarriage of just 2–4% providing a live fetus was seen on scan at 7 to 10 weeks. Pregnancies without a growing fetus are very likely to show signs of hormone deficiency but clearly the miscarriage is already inevitable. Such low rates of miscarriage after a live fetus has been identified compare with the generally accepted rates of 15–20% in clinically recognized pregnancies.

Chromosome analysis of fetal tissue obtained at miscarriage has shown that between 50 and 60% of fetuses have a chromosome anomaly (Boué *et al.* 1975; Lauritsen 1976). Such defects presumably occur around ovulation and fertilization and although abnormalities in the hormonal control of ovulation might be one factor, it seems increasingly obvious that any hormonal factor associated with miscarriage is not a simple progesterone deficiency.

So despite many years of intensive research there is no satisfactory evidence of any specific benefit from progesterone treatment. This need not deter future prospective research designed to assess the importance of corpus luteum deficiency and progesterone levels in early pregnancy in relation to the observed frequency of miscarriage, but any new treatment trials must be randomized and include early and repeated ultrasound scans if we are to derive clinically useful information. The literature abounds with examples of useless treatment that has subsequently been shown to be harmful. Not all progestogens are harmless and in the absence of evidence of benefit their use in pregnancy should be abandoned.

Meanwhile the recommended clinical management would be as follows. After a miscarriage adequate time should be allowed for the resumption of regular menstruation and full psychological recovery. That also allows an opportunity for proper preconception counselling in relation to smoking, alcohol, diet and exercise, designed to improve the patient's general health and morale. A normal ultrasound scan early in the next pregnancy then gives the assurance of a success rate of around 95% or more. That should be followed by continued psychological support with repeated visits and assessment of progress. Placebo therapy may be required as well if there is a particularly bad history or persistent anxiety.

Whether any of these measures has any specific effect we do not know but in the light of current knowledge they seem sensible and they represent the continuing process of 'tender loving care'.

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Can social support influence pregnancy outcome?

The idea that pregnancy outcome can be favourbly affected by the provision of social support is hardly new, but the desire to test this hypothesis systematically is responsible for a new wave of studies currently in progress or reaching publication stage. As the American epidemiologist Berkman (1984) has noted, the message that 'a friend, not an apple a day, will keep the doctor away' may seem persuasive, but the faith placed in social support is akin to popular fondness for chicken soup—its efficacy is a matter of folk wisdom not of scientific evaluation. The important scientific question to be asked in relation to social support is whether it can be shown measurably to improve health. Under the broad heading of 'health', what need to be examined are, however, not only measures of physical health, but the extent to which individuals feel emotionally content, and able to make proper and appropriate use of the social and material resources available to them.

The paper in this issue by Spencer *et al.* (p. 281) reporting the South Manchester Family Worker Trial belongs to this new group of studies that assess the role of social, as distinct from clinical, care in promoting perinatal health. In this study lay workers were employed to provide a variety of services for childbearing women which are not normally part of what is meant by antenatal care. The family workers, selected 'on the basis of personality and general life experience' gave practical help in the form of advice on state benefits, assistance with housework and childcare, and generally provided a listening ear. However, the study's main aim of increasing mean birthweight and length of gestation was not achieved, despite the fact that experience of conducting the scheme 'strongly indicated that family workers increased the subjective well-being of their clients'.

The South Manchester Family Worker trial may be taken as evidence that social support is ineffective in promoting perinatal health. It is known that the interpretation, and particularly the translation into policy recommendations, of research findings may have more to do with the general climate of opinion than with the actual structure, organization and results of research (Stacey 1987). In this instance, it is important to ask a number of questions: first, what was the trial in fact assessing? Second, what are the likely constraints in terms of pregnant women's social, material and health circumstances, on the health-promoting potential of social support? Third, and most fundamentally, what is the state of the art of research designed to link social and medical models of childbearing?

In the South Manchester study over half the women allocated to the family worker group did not take up the offer. The trial is thus assessing the effects of *offering,* not of *receiving* family worker help. With the wisdom of hindsight, Spencer and her co-workers may regret the choice of pre-randomization consent, as post-randomization refusal effectively made it impossible for the study to examine the process and effectiveness of family worker help in those households where it was accepted. It is also to be regretted that the design of the trial contained no measures of pregnancy outcome other than mortality, birthweight and gestational age. The 'strong' indication of increased 'subjective well-being' of family worker clients might well have translated into quantifiable improved health outcomes.

The target population in this study was women at above average risk of adverse outcomes. This appears to be the general rule in a number of social support trials (Heins *et al.* 1986; Stanley & Bryce 1986; A. Oakley & L. Rajan 1988, unpublished observation), and raises interesting questions about the policy role social support researchers envisage for this form of care. Women at enhanced risk of a low-birthweight infant and other adverse pregnancy outcomes are known to be socially disadvantaged also. For this reason, various of the obstetric risk scoring systems in current use (including the eligibility criteria employed by Spencer *et al.*) include such measures as low social class, single/separated/divorced status and cigarette smoking. The argument for taking social risk into account is clearly that such women are those most in need of whatever help is available. Yet, and paradoxically, it is to be expected that social disadvantage will provide a weighty counter to any benefits to be obtained from a programme of social support (as it must also do in relation to the therapeutic effectiveness of clinical care).

It would be interesting to know, for example, to what extent in the South Manchester trial family workers' advice and help with financial benefits resulted in household income changes, and whether the family workers were able to have any impact on other aspects of pregnant women's social circumstances. Although social support may be fashionable, the funding agencies are not likely to look favourably on randomized control trials of income support—which is one of the many meanings given to this all-embracing term (Broadhead *et al.* 1983). The only randomized control trial to assess income maintenance in pregnant women did indicate some effect on particular subgroups, though unfortunately the design of the study makes its findings difficult to interpret (Kehrer & Wolin 1979).

Finally, with regard to the state of the art in this area of research, it has to be said that we are as yet only at the beginning of designing a way to study systematically the interaction of social and other factors. This applies both in terms of the interventions made (either in routine practice or under the heading of research) and in terms of how the results of such interventions are assessed. The mind–body divide—the separation of social and medical models of reproduction specifically and health and illness more generally—continues to prevail, despite considerable evidence that such a division is inappropriate (Oakley *et al.* 1982). Recent overviews of supportive social interventions in pregnancy unfortunately apply the same rule by treating the 'hard' outcomes of birthweight and gestational age as different classes of events from 'soft' outcomes such as maternal psychological well-being (Elbourne *et al.* 1989). The evidence of these overviews confirms the South Manchester trial finding of no demonstrable effect on birthweight and gestational age (though there are signs that social interventions may influence the rate of very low birthweight). It may well be that further well-designed and well-conducted trials confirm this conclusion. Until, and even when, we have a more complete picture, it needs to be remembered that the factors responsible for the time and the weight at which babies are born are complex and multifaceted, as is their interaction with one another.

There is no doubt, however, that social support improves the psychological health and satisfaction of the woman, as well as having a range of effects probably connected with this, including promoting breast-feeding and male domestic participation and reducing the occurrence of worrying health problems in babies (Elbourne *et al.* 1989; Oakley 1988; A. Oakley & L. Rajan 1988, unpublished observation). These effects themselves indicate the integration of psychosocial and physical health, as for example the increased emotional well-being of supported women facilitates breast-feeding, which in turn promotes the physical health of the infant, both in the short and the long term.

Social support research has never been a funding priority and seems increasingly unlikely to be so in countries such as the UK and the USA in the late 1980s. As such research attempts to bridge the gap between two models of health—the social and the medical—so it falls between the agendas of the social and medical funding agencies. At a time when it is generally admitted that there is both a crisis of confidence and a financial crisis in the professional health services of the industrialized world, this seems particularly regrettable. That kindness is cheap (or even free) is not the only reason for recommending investigation of its health-promoting potential—but it must surely be one such reason.

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Cordocentesis

The ability to obtain fetal blood during pregnancy without major risk to either the mother or her baby has provided obstetricians with an important new investigative technique. One of our abiding frustrations is the inaccessibility of our fetal patient, and anything that can be achieved to overcome this problem should be cautiously welcomed.

Initial attempts at blood sampling were relatively crude and included such techniques as placentesis (Fairweather *et al.* 1978) which not only produced samples often of mixed maternal and fetal blood but also appeared to be associated with fetal death in about 10% of cases.

The collection of fetal blood under direct vision was dependent on the development of fibre-optic technology and the production of a suitable fetoscope. The first percutaneous transabdominal fetoscopy was described by Hobbins in 1974 who used a 1·7-mm scope. The fetus was seen and blood was aspirated from the vessels crossing the placenta. Later, Rodeck & Campbell (1978) described a method both for looking at the fetus and for sampling fetal blood from vessels in the unbilical cord.

These methods seemed to offer considerable advantages since the fetal blood sample was likely to be pure and uncontaminated by either maternal blood or amniotic fluid. Further, the technique could be performed under sedation and local anaesthesia alone, and fetal haemorrhage was likely to be rare because of the small calibre of the needle.

Although the first attempts at sampling involved the placental vessels it became clear that those in the cord were preferable, being easier to approach when the placenta was anterior and much less prone to prolonged bleeding, probably because of the supporting Wharton's jelly. The vessels at the cord root seemed the easiest to use, the cord being tethered to the placenta at this point and so relatively immobile. Once a reliable method of accessing the fetal circulation had been found it became possible to use the technique as a means of introducing therapeutic agents, most commonly blood in severe rhesus disease, into the fetal circulation. The first intravascular transfusions were described by Rodeck in 1981 and the use of this technique as opposed to intraperitoneal transfusion has steadily gained ground ever since.

While fetoscopy proved to be a useful and, in skilled hands, relatively safe method by which to direct fetal blood sampling, improvements in ultrasound technology meant that it became possible to insert a needle, usually 20- or 22-gauge, into the umbilical vessels under ultrasound guidance. This technique was first described by Daffos *et al.* (1984) and called variously cordocentesis, ultrasound-guided needling or percutaneous umbilical blood sampling (PUBS). As for fetoscopy, the placental end of the cord is used so that the target is relatively fixed. The mothers do not usually require sedation and the procedure can be conducted on an outpatient basis in much the same way as an amniocentesis.

The results of the method described by Daffos *et al.* (1984) are impressive, with a usable fetal blood sample available at the first attempt in 97% of cases (Daffos *et al.* 1985) and a procedure time of <5 min in 70% of attempts. Other groups, with less experience, have also produced some encouraging figures, Weiner (1987) successfully obtaining a sample in 95% of patients.

The risks of cordocentesis for the mother appear to be negligible but they are difficult to determine for the fetus because they depend largely on the indications for the blood sample. Thus, many fetal anomalies will carry a grave prognosis, whereas for the fetus being investigated, for example, merely for a possible infection the prospects should be good. In the series described by Daffos *et al.* (1985), where the most frequent reason for fetal blood sampling (68%) was to investigate a potential toxoplasmal infection, the rate of miscarriage was 0·8% and of stillbirth was 1·1%. Of the four intrauterine deaths only one was considered to be procedure related. Expanded results from the same group (personal communication), which are derived from 1695 fetal blood samples, indicate a procedure-related loss of about 0·5% and a total loss of about 1·4%.

Figures from the Ninth Meeting of the International Fetoscopy Working Group in September 1987 (unpublished observations), which are accumulated over 1 year from all the members of the group, indicated that for the 1570 pregnancies in which this method of blood sampling was performed the overall loss rate was 7% (3·4% <28 weeks; 3·6% >28 weeks). Although these losses appear high they undoubtedly reflect the indications for which the fetal blood sample was obtained.

Under what circumstances is fetal blood sampling indicated? Probably in the UK the clearest indication is the need to obtain a rapid karyotype, usually when either a structural fetal anomaly or a condition such as non-immune fetal hydrops has been identified with ultrasound. The method also has an important role in the assessment of fetal anaemia in pregnancies complicated by rhesus isoimmunization, and there is also a miscellaneous group of indications such as fetal infection and, occasionally, coagulopathies such as haemophilia in which an earlier DNA diagnosis has not been possible.

More recently, interest has focused on the use of fetal blood sampling to assess blood gases in severe intrauterine growth retardation. The role of this technique in this circumstance remains unclear and although preliminary data were encouraging (Soothill *et al.* 1987), recent publications cast some doubt (Cox *et al.* 1988). This may reflect the fact that growth retardation is a complex and heterogeneous problem to which knowledge of the acid-base status of the fetus may contribute little. That said, the prospects of finding a biochemical factor that could be used to substantiate abnormal fetal biophysical observations antenatally would be of immense clinical value. No such factor is known at present and further work is required to improve our understanding of the pathophysiological basis of fetal growth retardation.

A final role for the procedure is in the treatment of the anaemic fetus. Although fetal blood sampling under ultrasound control is a major advance, the ability to perform transfusions directly into the fetal circulation is of vital importance. When fetoscopy was used to perform intravascular transfusions under direct vision, problems were sometimes encountered with the field of vision being obscured by blood leaking around the needle insertion. Repeat transfusions were also difficult, particularly later in pregnancy when the amniotic fluid was becoming coloured and murky. In contrast, ultrasound-guided procedures do not suffer from these difficulties and this is a distinct advantage particularly when multiple transfusions, set close together, are required in the severely anaemic and hydropic fetus. Worldwide experience of intravascular transfusions shows that this is an effective method of treating these very sick fetuses. Overall, data presented by the groups attending the Ninth International Fetoscopy Working Group showed that nearly half the 58 hydropic fetuses and 84% of the 147 non-hydropic fetuses survived.

The final question relates to who should perform these techniques and where they should be done. Without wishing to sound elitist, it is very likely that these specialized techniques should be gathered together in a few large centres throughout the country and probably in departments already providing a regional service for scanning fetal anomalies. Although the technique is similar to amniocentesis it is not as easy, and considerable experience is required to reliably obtain samples of pure fetal blood. Furthermore, there must be a well-defined procedure for dealing with the blood sample, and it is often forgotten that the success of these techniques depends upon a whole team of experts.

A personal view is that cordocentesis is an invaluable technique but one that must be used in the right circumstances and by the right personnel if it is not to fall into disrepute. There is no place for 'part-time' cordocentesis and any move in this direction should be discouraged. Unfortunately the risk that this may happen is higher than with fetoscopy, a technique for which the perceived level of danger and of skill required was higher.

Careful monitoring is essential and those performing cordocentesis must be both properly trained and able to maintain their expertise. For example, the unit in which they work should, perhaps, undertake no fewer than 30 cordocenteses a year. This is a service most appropriately provided in units specializing in fetal medicine.

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A meta-analysis of randomized control trials of progestational agents in pregnancy

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Summary. The continued use of progestational agents in attempts to achieve a normal outcome of pregnancy in women with a 'high-risk' pregnancy (previous miscarriage, stillbirth or present preterm labour) prompted this meta-analysis of randomized control trials of such therapy. Of 20 trials of a progestogen 15 had combinable data. Combined comparisons, using odds ratios with confidence intervals, were made of the rates of livebirths at term or preterm and the sum of term and preterm deliveries, miscarriages, stillbirths and neonatal deaths. All but one comparison failed to show a significant benefit. Only the preterm delivery versus the term delivery comparison approached statistical significance. There were average deficiencies of quality apparent in the studies, and a test for heterogeneity among the studies was positive, but these caveats do not diminish the conclusion that progestogens should not be used outside of randomized trials at present. If trials are done, they should include only women with demonstrated hormonal abnormalities who are carrying a live fetus as shown by ultrasonography.

It is generally accepted that the presence of progesterone is required for the maintenance of pregnancy; one need only look at any physiology or obstetrics text to learn about the relation between progesterone and the other hormones leading up to and maintaining pregnancy. Research into the existence of a pregnancy-maintaining hormone goes back to the turn of the century (Fraenkel 1903, 1910—cited in Allen & Corner 1929); the hypothesis that progesterone was in fact the hormone in question dates from the early 1950s (Bishop *et al.* 1950; Bishop & Richards 1952; Hoffman 1944—cited in Bishop *et al.* 1950).

Investigations on the action mechanism of progesterone are more recent, with some studies suggesting that progesterone exerts its action either through an inhibition of oxytocin-induced myometrial excitation (Fuchs & Fuchs 1958; Bengtsson & Csapo 1962; Fuchs & Koch 1963; Csapo *et al.* 1972) or through an inhibition of prostaglandin (PG) excitation (Csapo *et al.* 1974*a*, *b*) specifically, that of the $PGF_{2\alpha}$ subclass (Csapo 1976).

If, as those studies would lead us to believe,

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the presence of progesterone inhibits uterine contractions, then its absence should allow unopposed myometrial excitation leading to full-blown labour. Whereas some studies have not reported a decrease in plasma progesterone levels in the weeks preceding the onset of term labour (Johansson & Jonasson 1971; Tulchinsky *et al.* 1972; Kumar *et al.* 1964; Llauro *et al.* 1968; Yannone *et al.* 1968; Shaaban & Klopper 1973; Craft *et al.* 1969; Greig *et al.* 1962; Eton & Short 1960), others have found that plasma progesterone levels do in fact decrease in that time period (Csapo *et al.* 1971; Turnbull *et al.* 1974). With regard to the first group of studies, however, numerous questions have been raised as to their validity, thereby strengthening the findings of the latter group of studies.

As that body of knowledge was obtained, clinical researchers concerned with preventing major failures of pregnancy (miscarriage, unexplained stillbirth and preterm labour) attempted to establish a relation between plasma progesterone levels and failures of pregnancy. They argued that these pregnancy failures resulted from insufficient levels of plasma progesterone and that in women with high-risk pregnancies (a history of recurrent miscarriage, stillbirth, or preterm labour) these failures could be prevented by progesterone replacement therapy.

This paper is a meta-analysis of randomized control trials involving the use of progesterone and other progestogenic agents for the maintenance of pregnancy.

Materials and methods

An exhaustive search of the literature was performed. A preliminary list of papers was provided by the *Oxford Database of Perinatal Trials* (Chalmers *et al.* 1986). Papers were also searched for through the Bibliographic Retrieval Service (BRS) and the National Library of Medicine (NLM) computer systems based on medical subject heading key words (e.g. pregnancy, clinical trials, random allocation, double-blind method, progesterone, sex hormones), by routine searching of *Current Contents* (a weekly publication listing recently published articles by journal), and by searching the references of studies and review articles as they were obtained.

Papers to be included in this meta-analysis had to fulfill the following criteria:

(1) *Rationale for treatment.* All women must be considered 'high-risk' pregnancies.

(2) *Randomized control trial.* It must be explicitly stated within the text that patients were randomly or quasi-randomly (e.g. alternate patients) assigned to the treatment or control group.

(3) *Hormones.* The women must have received progesterone or one of its derivatives (natural or synthetic) during the pregnancy.

(4) *Results.* The paper must provide data on outcome of pregnancy with respect to frequency of livebirths and at least one of the following: miscarriage, stillbirth, or neonatal death.

Abstracts and review articles were not considered for analysis.

To minimize observer bias in the selection of studies to be analysed, the articles were gathered by an independent researcher. Once gathered, the papers were given a code number and the 'Methods' and 'Results' sections were separated and differentially photocopied by the same outside observer so as to blind the assessors to the journal of publication, author, and source of the study. The 'Results' sections were further blinded with respect to the treatment groups so that the data could be extracted in an unbiased manner. Once differentially copied, it was thus possible to assess objectively the quality of those sections following guidelines suggested previously (Chalmers *et al.* 1983; Liberati *et al.* 1986; Antczak *et al.* 1986). The method assesses details of study design, randomization, blinding, data presentation and analysis, and assigns a score between 0·0 and 1·00.

Each section of every paper was separately graded by two reviewers (P.G. and either T.C.C. or H.S.S.). Differences in either the quality grading of a paper or in the selection judgement (i.e. the inclusion or exclusion of a paper for analysis) were settled in conference.

There were five possible outcomes for any given pregnancy: miscarriage (MIS), neonatal death (NND), stillbirth (SB), preterm delivery (PD), or term delivery (TD). In the case of a twin pregnancy, more than one outcome was possible. For the purpose of this paper, all reported outcomes were accepted as such unless both reviewers felt that a given outcome had been either incorrectly classified or could be more accurately described. Recognizing a worldwide variability in exact definitions of outcomes (Mugford 1983), and a lack of definitions in the papers analysed, the following definitions were adopted:

Miscarriage—a fetal death before 28 completed weeks gestation.

Neonatal death—any infant death that occurred within 28 days following livebirth.

Stillbirth—the birth of a dead fetus after 28 completed weeks gestation.

Preterm delivery—the birth of a live infant either before 37 completed weeks gestation or with a birthweight of <2500 g.

Term delivery—the birth of a live infant with a birthweight of >2499 g after 37 completed weeks gestation.

After all the papers were graded and all pertinent data extracted, the codes were broken. The data from each study were assembled into '2×2' tables (treatment/control *vs* negative/positive outcome) and these tables were then combined statistically according to a modification of the Mantel–Haenszel technique (Yusuf *et al.* 1985), yielding a ratio of the odds of a positive outcome on control compared with treatment.

To avoid committing a type II error, that is, failing to observe a significant difference between two groups when such a difference does, in fact, exist (in this case due to over-collapsing of test groups), the following eight outcome comparisons were made:

Negative (miscarriage + stillbirth + neonatal death) *vs* live (preterm + term delivery) (one comparison).

Miscarriage or stillbirth or neonatal death *vs* live (three comparisons).

Miscarriage or stillbirth or neonatal death or preterm delivery *vs* term delivery (four comparisons).

When no specific data were provided regarding a single outcome, we inferred by adding all other outcomes (except in the case of neonatal death since some studies provided no follow-up data). Thus, if a study of *n* women reported *x* miscarriages, *y* preterm deliveries and *z* term deliveries and the sum of those outcomes was equal to *n*, then the assumption was made that there were zero stillbirths.

In many of the studies, the number of patients finally analysed did not equal the number of patients randomized due to withdrawals during the course of the study. To assess whether those withdrawals could have biased the outcome of the studies, a sensitivity analysis was performed. Most studies provided data on the total number of patients randomized to each group, as well as on how many patients withdrew from each; if the former information was not provided, it was assumed that there had been an equal initial distribution of patients. For a 'best case' analysis (i.e. treatment was effective), treated patients whose outcome was unknown were assumed to have had adverse outcomes at one-half the rate of those whose outcome was known. For a 'worst case' analysis, treated patients whose outcome was unknown were assumed to have had adverse outcomes at twice the rate of those whose outcome was known. For both analyses, control patients whose outcome was unknown were assumed to have had outcomes at the same rate as control patients whose outcome was known.

Results

The literature search yielded 31 randomized control trials, 35 non-randomized control trials, 36 reviews/editorials, 60 follow-ups, and 16 miscellaneous papers. Studies of progestogens employed as tocolytic agents around term were excluded from this meta-analysis. Of the 31 randomized control trials 20 tested a progestogen, six tested an oestrogen, two tested both an oestrogen and a progestogen concomitantly, two tested hCG, and one tested an androgen.

Of the 20 trials testing a progestogen five were excluded from the present analysis One (Govaerts-Videtsky *et al.* 1965) was excluded because it was ongoing at the time of publication; although it reported no differences between the treatment and control groups, the assignment codes had not been broken, making it impossible to use the data in a pooled analysis. Three other reports could not be included because of insufficient data (Turner *et al.* 1966) or failure to report data on the outcome of pregnancy (Erny *et al.* 1986; Souka *et al.* 1980). A fifth did not break the code initially (Shearman & Garrett 1963) and later only the number of miscarriages was given (Shearman 1968); these data were not included in our analysis because the outcomes for those patients who did not miscarry were unknown. For the sake of thoroughness, however, the data were pooled with the original 15 randomized control trials based on the assumption that in those women who did not miscarry the pregnancy continued normally to produce one live infant; their inclusion did not alter the outcome of the original calculations.

Although one study tested both allyloestrenol (a progestogen of the 19-nortestosterone series without androgenic effects) and 17-alpha-hydroxyprogesterone caproate (17-OH-PC) without identifying which patients received which drug (Tognoni *et al.* 1980), it was included in this meta-analysis because both agents were progestogens. Also, one study (Moller & Fuchs 1965) provided data on 'foetal salvage' (live-births), but did not differentiate data for negative outcomes into treated and control groups; therefore, these data were only included in the overall negative *vs* live analysis.

Thus, 15 randomized control trials were included in this meta-analysis, 12 of them were identified through the *Oxford Database of Perinatal Trials* (Chalmers *et al.* 1986) and one each was identified through *Current Contents,* National Library of Medicine computer search, and published references. The main features of these studies are shown in Table 1.

The individual and combined results are shown in Table 2, where they are arranged in descending order of quality score. The mean quality score of these 15 papers, out of a possible score of 1·00, was 0·40 (SD 0·15). For 376 trials graded according to this method (including this set of trials), the overall mean is 0·42 (SD 0·17) (D. Reitman, H. S. Sacks & T. C. Chalmers, Technical quality assessment of randomized control trials. Presented at the 8th Annual Meeting of the Society for Clinical Trials, 17–20 May 1987, Atlanta, GA, USA). Therefore, the graded papers included in the present analysis are of similar quality as other papers graded by T. C. Chalmers and co-workers over the past 10 years.

In those studies that mentioned them, no statistically significant maternal or fetal side-effects of progestogen therapy were observed (two of the studies failed to mention side-effects at all). One study examined twin pregnancies (Hartikainen-Sorri *et al.* 1980) and reported that infants treated with progesterone had just over twice the frequency of respiratory problems as did control infants (statistical significance was not reported). Since some of these twin pregnancies had different outcomes (e.g. one twin a miscarriage, one twin a term birth), all twin pregnancies in this study were considered to have had two individual outcomes.

The progestogens did not appear to have an

Table 1. Studies included in the meta-analysis, listed in decreasing order of quality score. In all instances the control patients received no hormonal therapy

Study	Randomization blinded	Placebo	Regimen	Dosage	Gestation at start of therapy (weeks)
Johnson *et al.* (1975)	Yes	Yes	17-OH-PC*	250 mg/week	16·7±4·4
Papiernik-Berkhauer (1970)	Unknown	Yes	OHPC†	Unknown	Unknown
Hartikainen-Sorri *et al.* (1980)	Unknown	Yes	17-OH-PC	250 mg/week	29·2±1·9
Sondergaard *et al.* (1985)	Unknown	Yes	Progest‡	200 mg/day	<11
Yemini *et al.* (1985)	No	Yes	17-OH-PC	250 mg/week	12·2±3·3
Klopper & MacNaughton (1965)	Yes	Yes	EL§	100 mg/day	<10
Hauth *et al.* (1983)	Unknown	Yes	17-OH-PC	100 mg/week	16–20
Fuchs & Stakemann (1966)	No	Yes	Progest	Schedule	21–36
LeVine (1964)	No	Yes	17-OH-PC	500 mg/week	<17
Dalton (1962)	No	No	Progest	Schedule	16–28
Goldzieher (1964)	Yes	Yes	MAP‖	10 mg/day	<18
Brenner & Hendricks (1962)	Unknown	Yes	MAP	80 mg/day	36–38
Moller & Fuchs (1965)	No	Yes	MAP	Schedule	8–21+
Swyer & Daley (1953)	No+unknown	No	Progest	150-mg implant	<11
Tognoni *et al.* (1980)	Unknown	Yes	OHPC/AE**	OHPC—25 mg/day AE—10 mg/day	<15

* 17-OH-PC=17-alpha-hydroxyprogesterone caproate.
†OHPC=hydroxyprogesterone caproate.
‡Progest=Progesterone.
§EL=Enol Luteovis (Vister), a cyclopentyl enol ether of progesterone.
‖MAP=6-alpha-17-alpha-acetoprogesterone (medroxyprogesterone acetate).
**AE=Allyloestrenol (a progestogen of the 19-nortestosterone series without androgenic properties).

Table 2. Results of the individual studies included in the meta-analysis Listed in order of decreasing quality score

				Outcome											
		No. of patients		TD		PD†		Live		MIS		SB		NND	
Study	Regimen*	Rand	Anal.	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Johnson	17-OH-PC	23	18	18	(100)	0	(0·0)	18	(100)	0	(0·0)	0	(0·0)	0	(0 0)
et al (1975)‡	Control	27	25	10	(40·0)	9	(36 0)	19	(76·0)	4	(16·0)	1	(4·0)	2	(8·0)
Total		50	43												
Papiernik-	OH-PC	50	49	47	(95 9)	2	(4·1)	49	(100)	0	(0·0)	0	(0·0)		—
Berkhauer (1970)	Control	49	48	39	(81·3)	9	(18·8)	48	(100)	0	(0·0)	0	(0·0)		—
Total		99	97												
Hartikainen-Sorri	17-OH-PC	78	78	44	(56·4)	24	(30·8)‖	68	(87·2)	0	(0·0)	1	(1·3)	3	(3·8)
et al. (1980)§	Control	76	76	56	(73·7)	18	(23·7)	74	(97·4)	0	(0·0)	1	(1·3)	1	(1·3)
Total		154	154												
Sondergaard	Progest	—	23	6	(26·1)	0	(0·0)	6	(26·1)	17	(73·9)	0	(0·0)		—
et al. (1985)	Control	—	19	2	(10·5)	0	(0·0)	2	(10·5)	17	(89·5)	0	(0·0)		—
Total		143	42												
Yemini	17-OH-PC	—	39	26	(66·7)	5	(12·8)	31	(79 5)	8	(20 5)	0	(0·0)	0	(0·0)
et al (1985)	Control	—	40	23	(57·5)	14	(35 0)	37	(92 5)	3	(7 5)	0	(0·0)	0	(0·0)
Total		80	79												
Klopper & Mac-	EL	18	18		—		—	10	(55 6)	8	(44 4)	0	(0·0)		—
Naughton (1965)	Control	15	15		—		—	10	(66·7)	5	(33·3)	0	(0·0)		—
Total		33	33												
Hauth	17-OH-PC	80	80	71	(88·8)	6	(7·5)	77	(96·3)	0	(0·0)	1	(1·3)	2	(2·5)
et al. (1983)	Control	88	88	77	(87·5)	8	(9·1)	85	(96·6)	0	(0·0)	3	(3·4)	0	(0·0)
Total		168	168												
Fuchs &	Progest	—	63	28	(44·4)	35	(55·6)	63	(100)	0	(0 0)	0	(0·0)		—
Stakemann (1960)	Control	—	63	28	(44·4)	33	(52 4)	61	(96 8)	0	(0 0)	2	(3·2)		—
Total		150	126												
LeVine (1964)	17-OH-PC	—	15	8	(53 3)	3	(20·0)	11	(73·3)	3	(20·0)	0	(0 0)	1	(6·7)
	Control	—	14	4	(28·6)	3	(21·4)	7	(50·0)	7	(50·0)	0	(0 0)	0	(0·0)
Total		56	29												
Dalton (1962)	Progest	76	62		—		—	61	(98·4)	0	(0·0)	1	(1·6)**	0	(0·0)**
	Control	74	66		—		—	63	(95·5)	0	(0·0)	3	(4·5)**		
Total		150	128												
Goldzieher (1964)	MAP	23	23	18	(78·3)	0	(0·0)	18	(78·3)	5	(21 7)	0	(0 0)		—
	Control	31	31	26	(83·9)	0	(0·0)	26	(83·9)	5	(16·1)	0	(0·0)		—
Total		54	54												
Brenner &	MAP	—	97		—		—	96	(99·0)	0	(0·0)	0	(0·0)	1	(1·0)
Hendricks (1962)‡	Control	—	98		—		—	98	(100·0)	0	(0·0)	1	(1 0)	0	(0 0)
Total		200	195												
Moller &	MAP	—	123		—		—	60	(48·8)		—		—		—
Fuchs (1965)††	Control	—	137		—		—	71	(51·8)		—		—		—
Total		—	260												
Swyer &	Progest	60	60	47	(78·3)	1	(1·7)	48	(80·0)	11	(18 3)	0	(0·0)	1	(1·7)
Daley (1953)	Control	53	53	39	(73·6)	1	(1·9)	40	(75·5)	13	(24·5)	0	(0 0)	0	(0 0)
Total		113	113												
Tognoni	OHPC/AE	74	71		—		—	45	(63 4)	26	(36·6)	0	(0 0)		—
et al (1980)	Control	71	68		—		—	47	(69 1)	21	(30·9)	0	(0·0)		—
Total		145	139												
TOTAL	Treated	—	819		—		—	661	(80 7)	78	(9·5)	2	(0 2)	8	(1)
	Control	—	841		—		—	688	(81·8)	75	(8·9)	8	(1)	3	(0·4)

Rand., Randomized, Anal , analysed

TD=term delivery (livebirth after 37 completed weeks gestation, birthweight ≥2500 g)

PD=preterm delivery (livebirth before 37 completed weeks gestation or birthweight <2500g).

Live=sum of TD+PD

MIS=miscarriage before 28 completed weeks

SB=stillbirth (birth of dead fetus after 28 completed weeks gestation)

NND=neonatal death (infant death within 28 days of livebirth)

* See Table 1 for key to drug abbreviations

† If preterm deliveries were listed by both gestational age and birthweight, the greater number was chosen for analysis.

‡ The sum of the outcomes is greater than the no of patients analysed due to multiple births

§ The numbers for Patients Randomized/Analysed have been doubled as each birth was treated as a discrete endpoint because not all pregnancies had identical outcomes

‖ Does not include three pregnancies (six endpoints) that were induced for medical reasons

** Only combined data for stillbirths and neonatal deaths were provided for controls, totals for SB and NND do not include these data

†† The sum of the outcomes is less than the no of patients analysed as no additional data were presented

impact on the outcome of pregnancy. There were fewer than one-half the number of neonatal deaths (NND) in the combined control group than in the combined progestogen-treated group and conversely fewer than one-half the number of stillbirths (SB) in the progestogen-treated group than in the control group; both of these differences are probably a reflection of the very low rates.

The combined comparisons of all negative versus all positive (live) outcomes, as well as various subgroup outcomes (as evaluated by Chi-squares and odds ratios with the 95% CI), are listed in Table 3. Some of the point estimates for the odds ratios were greater than 1·00 (suggesting a deleterious effect) and some were less than 1·00 (suggesting a beneficial effect). However, none of the χ^2 values was significant (P>0·05) and all confidence intervals overlapped 1·00, indicating that no statistically significant effect of the treatment could be detected. The chance of an interesting effect only seems possible in the case of the rather unusual comparison of preterm *vs* term deliveries.

In nine of the 15 studies included for analysis in the present study, the number of patients finally analysed did not equal the number of patients randomized because of the withdrawal of patients during the course of the studies. To assess whether withdrawals biased the outcome of these nine studies, a sensitivity analysis was performed.

For progestogen treatment, the 'best case' analysis of withdrawals, when applied to the negative *vs* live comparison (Table 3), significantly altered the overall outcome as indicated by the odds ratio (0·67; 95% CI 0·52 to 0·87) and χ^2 8·74 (P<0·01). The 'worst case' analysis of withdrawals raised the odds ratio from 0·88 to 0·96 (95% CI 0·74 to 1·26; χ^2 0·04). The 'best case' results imply that the possibility exists that such treatment may be beneficial, but the assumptions made for this analysis were very favourable.

A statistically significant value for χ^2 (24·56, P<0·05) was observed for the heterogeneity of the pooled progestogen studies. Possible sources of this variability include the use of different forms of progesterone when one or more could truly be effective or harmful, the varying study sizes, and the more than 30-year time-span over which the studies were conducted.

Because of the positive test for heterogeneity the data were reanalysed using the random effects method of DerSimonian & Laird (1986). These analyses, in which the confidence intervals are enlarged by their partial dependence on the between-study variability, did not change the overall conclusions.

Because of the possibility that the randomized control trials may not have been sensitive enough to pick up an effect of progesterone when given early in pregnancy, the studies listed in Table 1 were ranked according to the shortest gestational age at the start of progesterone therapy. The pooled odds ratio of the top seven papers with regard to the rates of miscarriage and livebirths was 0·906 (95% CI 0·592 to 1·387). There was thus no evidence of the studies having missed an early effect of progesterone.

Discussion

The present study has attempted to assess the role of progesterone and its analogues in the

Table 3. Pooled odds ratios of 15 randomized control trials using a progestogen for the maintenance of pregnancy

Analysis	No of studies*	χ^2§	Odds ratio	(95% CI on odds ratio)
Neg† *vs* Live‡	15	0·86	0·88	(0·66 to 1·15)
MIS *vs* Live	14	0·0027	0·97	(0·65 to 1·44)
SB *vs* Live	13	1·47	0·50	(0·2 to 1·28)
NND *vs* Live	7	1·41	2·37	(0·75 to 7·4)
MIS *vs* Term	8	0·76	0·75	(0·42 to 1·31)
SB *vs* Term	8	1·34	0·44	(0·15 to 1·34)
NND *vs* Term	6	0·51	1·89	(0·56 to 6·35)
PD *vs* Term	10	3·05	0·71	(0·49 to 1·02)

* Studies—studies were included only in those analyses for which they provided data, either directly or indirectly

† Negative—the sum of all miscarriages, stillbirths and neonatal deaths.

‡ Live—The sum of all preterm and term deliveries.

§ P>0·05.

maintenance of pregnancy. The progestogens appear to be ineffective.

Two studies (Medical Research Council 1955; Berle & Behnke 1977), which were excluded from our meta-analysis because a progestogen and an oestrogen were administered concomitantly to all treated patients, were pooled with the original 15 trials to see if it would make a difference in our results. Their inclusion did not alter the outcome of the original calculations.

A very large randomized control trial might establish the worth of progestogens in maintaining pregnancy, although the data in this study suggest that the case for their use could be considered closed. The Federal Food and Drug Administration in the 22 July 1977 issue of the Federal Register (cited in Chez 1978) announced that, due to a lack of sufficient evidence and possible increase in the risk of malformation, the use of progestational agents (including 19-nortestosterone derivatives, C-21 substituted progestins, 17 alpha-hydroxyprogesterone, and progesterone) for the prevention of recurrent miscarriage or the treatment of threatened miscarriage was not recommended. Yet a perusal of 11 medical textbooks (published since 1980) pertaining to obstetrics, pregnancy, and reproductive endocrinology revealed that progesterone replacement therapy remains an unsettled issue. A number of authors (Schulman & Chandra 1980; Dodson 1980; Crenshaw & Miller 1983; Hertz 1984*a*) made qualified recommendations for the use of a progestogen for the maintenance of pregnancy; three (Percival 1980; Niswander 1981; Henzl 1986) considered its use to be inappropriate, and five (Oxon 1980; Rivlin *et al.* 1982; Fuchs & Klopper 1983; Rayburn & Lavin 1984; Macdonald 1985) made no recommendations for or against its use.

Furthermore, as of 1980, the proportion of progestogens prescribed prophylactically for the maintenance of pregnancy ranged from 3% in the UK to 28% in Italy, with West Germany, the Netherlands, and France falling in between (Tognoni *et al.* 1980). Additionally, one in six general practitioners in England indicated in a recent survey that they still use a progestogen in this manner (Everett *et al.* 1987).

In contrast to our findings, Daya (this issue of the journal, p. 275) has suggested that in the specific subgroup of women with recurrent miscarriage, the aetiology of the pregnancy loss is a progesterone deficiency which could, at least in theory, be corrected with treatment. Daya argued that since the corpus luteum was the principal source of progesterone during the early stages of pregnancy, and since defects of the corpus luteum had been successfully treated with progesterone replacement, a woman with a history of recurrent miscarriage was at risk for a luteal defect. This could lead to decreased progesterone production, which in turn could be ameliorated with progesterone replacement therapy. Daya found a significant effect only in those randomized control trials which included patients with a history of three or more miscarriages treated with a progestogen. In none of the three studies included by Daya (Swyer & Daley 1953; Goldzieher 1964; LeVine 1964) was a significant progesterone deficiency actually demonstrated either in the treated or control patients (as evidenced by pregnanediol excretion).

The combined data from these three studies are less impressive when one examines the rate of term livebirths (Table 2). Furthermore, the three studies are in the lower half of the 15 studies in our meta-analysis by our quality scoring system. The selection of a subgroup without physiological evidence of distinction raises the problem of data-dredging when considering statistical significance. Moreover, seven of the 15 papers found by us admitted patients who had had two or more miscarriages. Analysis of these revealed no suggestion of effect (odds ratio 1·02, 95% CI 0·70 to 1·50), but the power to demonstrate a difference is small.

In addition to the question of efficacy, there is also the question of side-effects. To date, only the patients randomized by Dalton (1962) have been assessed retrospectively in this regard, and the findings have been conflicting, possibly due to the inclusion of non-randomized patients in the follow-up studies (Dalton 1976; Lynch *et al.* 1978; Lynch & Mychalkiw 1978).

A number of anecdotal and uncontrolled follow-up studies have been published suggesting that exposure *in utero* to exogenous progestogens may increase the risk of oesophageal atresia (Lammer & Cordero 1986); cardiac, neurological, neural tube and other major malformations in children whose mothers received either a progestogen or oestrogen (Nora *et al.* 1978), and 'tomboyishness' in girls (Ehrhardt & Money 1967). Data on 50 282 pregnancies from the Collaborative Perinatal Project (Heinonen *et al.* 1977*a*) indicated that 1399 (2·8%) of the women had received progestational agents and 866 of them took the drug during the first 4 lunar months of pregnancy. This latter group of women gave birth to 75 malformed children (standardized relative risk 1·04, 95% CI 0·79 to 1·36), with cardiac malformations occurring at a statistically significant increased rate (standardized relative risk 1·80, 95% CI 1·04 to 1·44) (Heinonen *et al.* 1977*b*). Other studies, however, have failed to detect these possible adverse effects (Katz *et al.* 1985; Varma & Morsman 1982; Uher *et al.* 1965; Kester *et al.* 1980), thus leaving the question of safety unanswered.

The advent of ultrasonography changes sharply the design requirements of future randomized control trials of agents for the prevention of miscarriage and preterm birth. Fetal death can be predicted with reasonable accuracy (Robinson 1975; Anderson 1980; Hertz 1984*b*; Nyberg *et al.* 1986; Scott *et al.* 1987) so that trials can be limited to situations in which the fetus has some chance of surviving. The lower rate of miscarriage in this subgroup of patients with threatened miscarriage will, however, require much larger studies.

In conclusion, this meta-analysis has failed to provide convincing evidence of the efficacy of progestational agents for the maintenance of pregnancy, and questions remain as to the extent of second generation side-effects. Since there is evidence of hormonal imbalance in some women with recurrent miscarriage, randomized control trials of new and more promising agents (other than progestogens) are still called for. These studies should be both large and numerous, and should include ultrasound screening for a live fetus.

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Efficacy of progesterone support for pregnancy in women with recurrent miscarriage. A meta-analysis of controlled trials

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Summary. Progesterone appears to be necessary to support an early pregnancy, and it has been used for this purpose for several decades. Its potential role in women with recurrent miscarriage due to luteal phase deficiency has been suggested, but its efficacy has not yet been demonstrated. Three controlled trials of progesterone treatment in women with recurrent miscarriage have shown small, but not statistically significant, increases in the rates of pregnancies that continue beyond 20 weeks in the treated groups. None of these studies had sufficient statistical power to detect a clinically significant improvement in outcome but pooling the results of these studies using the principles of meta-analysis has allowed an overall effect of treatment to be calculated. The resulting odds ratio for pregnancies reaching at least 20 weeks gestation was 3·09 (95% CI 1·28 to 7·42) which indicates that there is evidence to support the suggestion that progesterone given in early pregnancy is useful in women with recurrent miscarriage. Although, before progesterone is used in this way its efficacy in women with recurrent miscarriage due to luteal phase deficiency must be assessed in prospective double-blind randomized controlled trials mounted in the light of the results of this meta-analysis.

Progesterone appears to be necessary for implantation and maintenance of an early intrauterine pregnancy. The importance of the corpus luteum in pregnancy maintenance was demonstrated by experiments in which its removal in early pregnancy resulted in miscarriage which could be prevented by progesterone support. Seven of 11 patients subjected to luteectomy in the early first trimester of pregnancy demonstrated a decrease in plasma progesterone levels and miscarried within 7 days of surgery, compared with none of seven patients who were luteectomized and treated with daily injections of progesterone (Csapo *et al.* 1973).

Luteal phase defect is an entity in which the corpus luteum produces suboptimal amounts of progesterone resulting in retarded endometrial development (Jones *et al.* 1974; Daya *et al* 1988). The diagnosis is confirmed by endometrial biopsy in which a delay in development of more than 2 days is present in at least two cycles. Up to 40% of women with recurrent miscarriage (three or more consecutive miscarriages) have been shown to have luteal phase defects which presumably account for their recurrent pregnancy losses (Daya *et al.* 1988).

Progesterone has been used prophylactically and therapeutically for over 30 years, although there have been no controlled trials of progesterone efficacy in women with recurrent mis-

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carriage due to luteal phase defect. In contrast, there have been many case-control and randomized controlled trials of progesterone treatment in women with threatened miscarriage or a history of recurrent pregnancy loss. The controlled trials did not demonstrate that progesterone was beneficial in such patients, but the studies often contained both subgroups of women with a history of either recurrent or sporadic miscarriage. In view of the high prevalence of luteal phase defects reported in women with recurrent miscarriage, it is possible that a beneficial effect of progesterone in these patients was obscured by a large number of patients with sporadic miscarriage in whom progesterone treatment would probably not be beneficial.

The purpose of this study was to conduct a meta-analysis of controlled trials of progesterone given to women with a history of recurrent miscarriage in order to obtain an overall estimate of the effect of treatment on successful pregnancy outcome in this subgroup.

Materials and methods

Several sources were utilized to identify a list of clinical trials which could be selected for analysis. A search using the National Library of Medicine MEDLINE database covering the period 1966–1987 was conducted using the following Medical Subject Heading key words: pregnancy, progesterone, pregnancy complications, luteal phase, habitual abortion (recurrent miscarriage), research design and clinical trials. 'Random' was used as a text word and the search was limited to human studies. A list of publications was obtained from the *Oxford Database of Perinatal Trials* (Chalmers 1988). The Science Citation files were also searched using two key articles as tracers (Noyes *et al.* 1950; Jones & Delfs 1951). The reference sections of published studies and review articles on the use of progesterone in women with pregnancy complications were scanned for references that might be suitable. Finally, abstracts presented at scientific meetings were perused and some of the author's colleagues who are familiar with this area of reproductive medicine were consulted for any additional references.

The following definitions were used for this study:

Miscarriage. This was defined as a spontaneous loss of an intrauterine pregnancy at ≤20 weeks gestation, calculated from the first day of the last menstrual period.

Recurrent miscarriage. This was defined as three or more consecutive miscarriages.

Continuing pregnancy. This was defined as an intrauterine pregnancy that had advanced beyond 20 weeks gestation.

Studies of progesterone treatment were considered for analysis if they had at least one of the following in their design: random allocation, double-blind, placebo used as control, and patients with a history of recurrent miscarriage. To minimize bias in the selection of studies to be analysed, the papers were independently assessed by a colleague who is an infertility specialist in the Department of Obstetrics and Gynecology at McMaster University. Agreement analysis was performed between his assessment and the author's assessment using Cohen's kappa statistic.

Published trials were included in the analysis if:

(a) Patients were allocated to the treatment or control groups on a random or quasi-random (e.g. alternate) basis.

(b) Treatment with progesterone (either natural or synthetic) was started in the first trimester.

(c) The control group of patients had received placebo.

Trials were excluded from the analysis if patients who were treated did not have a history of recurrent miscarriage, or if there were insufficient outcome data to enable statistical comparison and integration of the findings.

Using the searching methods described, 34 studies were obtained. Most of these reports were cohort studies or case-control studies and several seemed to demonstrate a beneficial effect of treatment. Fifteen studies (Goldzieher 1964; Govaerts-Videtzky *et al.* 1965; Klopper & MacNaughton 1965; LeVine 1964; Shearman & Garrett 1963; Sondergaard *et al.* 1985; Swyer & Daley 1953; Tognoni *et al.* 1980; Varma & Morsman 1982; Yemini *et al.* 1985; Souka *et al.* 1980; Burton & Wachtel 1967; Morgan *et al.* 1960; Gerhard *et al.* 1987; Bishop *et al.* 1950) met the inclusion criteria for assessment, and the interobserver agreement on these studies produced an estimated kappa value of 0·81 (95% CI 0·64 to 0·98). After discussion, the disagreement between observers was resolved. Only 11 of

Table 1. Design features of controlled studies in progesterone treatment

Author (year)	Random allocation	Double-blind	Progesterone treatment	Placebo control	History of recurrent miscarriage
Goldzieher (1964)	+	+	+	+	+
LeVine (1964)	A	+	+	+	+
Klopper & MacNaughton (1965)	+	+	+	+	+
Yemini *et al.* (1985)	+	+	+	+	+
Shearman & Garrett (1963)	?	+	+	+	+
Swyer & Daley (1953)	+/A	?	+	+	+
Govaerts-Videtzky *et al.* (1965)	+	+	+	+	−
Sondergaard *et al.* (1985)	+	+	+	+	−
Gerhard *et al.* (1987)	+	+	+	+	−
Tognoni *et al.* (1980)	+	−	+	+	−
Souka *et al* (1980)	+	−	+	+	−

+, Yes; −, no; ?, not indicated; A, alternate

these studies (shown in Table 1) had random allocation or double-blind assignment, or both, of patients to treatment and control groups. Five of these studies were excluded as they were reports on patients with threatened miscarriage and with no previous history of recurrent miscarriage (Govaerts-Videtsky *et al.* 1965; Sondergaard *et al.* 1985; Varma & Morsman 1982; Souka *et al.* 1980; Gerhard *et al.* 1987). The remaining six studies were all conducted as randomized controlled trials on patients with a history of recurrent miscarriage. However, three of these six studies had to be excluded because data on patients with habitual miscarriage were not available (even after contacting the authors) to allow meaningful comparison and possible integration of the findings (Klopper & MacNaughton 1965; Shearman & Garrett 1963; Yemini *et al.* 1985). This left three studies which met the inclusion and exclusion criteria for the analysis and they were statistically combined (Goldzieher 1964; LeVine 1964; Swyer & Daley 1953).

Statistical analysis

Outcome data for patients with three or more miscarriages were extracted from the papers that were selected for analysis. The effect of treatment was defined as a difference in the proportion of patients achieving a continuing pregnancy (≥20 weeks gestation) with progesterone, compared with a control group of patients receiving placebo. Treatment effect was also expressed as an odds ratio together with its 95% CI. The test described by Mantel & Haenszel (1959) was used to provide an overall estimate of the effect of treatment and for testing the overall association. The null hypothesis underlying the overall test of association was that the overall odds ratio was equal to one. Before combining the individual studies, a formal test of homogeneity of treatment effect across the studies was performed using the method described by Breslow & Day (1980).

Results

The main features of the three studies available for analysis are shown in Table 2. All suggested a beneficial effect of treatment, a 15–33% increase in the proportion of pregnancies continuing beyond 20 weeks, but in none of the studies was the difference between the experimental groups statistically significant. In order to combine the individual trials, consistency of treatment effect across trials was tested using the test described by Breslow & Day (1980), and no significant lack of homogeneity (P=0·81) was demonstrated. This indicated that no trial had a significant treatment effect worse or better than the overall treatment effect. The individual odds ratios in each of the trials also indicated a slight preference for progesterone treatment (Table 2). However, the 95% CI on these odds ratios were too wide to produce statistical significance. After pooling the trials using the Mantel–Haenszel (1959) technique to estimate the overall effect of treatment, an odds ratio of 3·09 was obtained (Table 2). The 95% CI around this estimate excludes 1·0, thus providing evidence of an association between treatment and outcome (Table 2, Fig. 1).

Table 2. Effect of progesterone treatment on continuing pregnancy rate

No.	Trial	Progestogen	Continuing pregnancy rate: Treatment	Continuing pregnancy rate: Control	Treatment effect‡ (%)	(95% CI on treatment effect)	P*	Odds ratio	(95% CI on odds ratio)
1	Swyer & Daley (1953)	MPA	21/27 (77·8%)	11/20 (55·0%)	22·8	(8·1 to 49·3)	0·10	2·86	(0·69 to 12·37)
2	Goldzieher (1964)	17-OHP-C	6/8 (75·0%)	6/10 (60·0%)	15·0	(−36·4 to 51·3)	0 51	2·00	(0·18 to 25·01)
3	LeVine (1964)	PP	12/15 (80·0%)	7/15 (46·7%)	33·3	(−7·7 to 61·4)	0·06	4·57	(0·72 to 32·52)
Overall odds ratio†								3·09	(1·28 to 7·42)

*χ^2 test on 1 d.f.

†Overall test of association using Mantel–Haenszel χ^2-test on 1 d.f. = 6·20 ($P<0·01$).

‡Treatment effect is the difference in proportions of successful pregnancy between treatment and control groups.

MPA, Medroxyprogesterone acetate; 17-OHP-C, 17-hydroxyprogesterone caproate; PP, progesterone pellet implants.

Discussion

Many studies in patients with recurrent miscarriage due to luteal phase defect have indicated a beneficial effect of progesterone, but no randomized controlled trials have yet been conducted (Grant *et al.* 1959; Balasch *et al.* 1986; Daya *et al.* 1988). The results of the meta-analysis in the present study indicate that progesterone administered in the first trimester to women with a history of recurrent miscarriage appears to be efficacious in improving the chances of the pregnancy advancing beyond 20 weeks gestation. Since there is a high prevalence of luteal phase defect in patients with recurrent miscarriage, and since progesterone treatment can correct the retardation in endometrial maturation, the demonstrated efficacy is most likely to be mediated through support of a corpus luteum with suboptimal function.

None of the trials had sufficient statistical power to detect a clinically significant treatment effect on its own. For example, in order to have a power of 80% to detect a 25% improvement in pregnancy rate with treatment (over a control pregnancy rate of 63%), and allowing for a type I error of 5%, a sample size of 88 patients is required. Thus, none of the studies had a sample size that was large enough to show this difference if it was present. But by combining the findings in the studies, the power was substantially improved and a statistically significant treatment effect was detected.

Studies are generally more likely to be published in professional journals if they demonstrate statistically significant findings (Dickersin *et al.* 1987). Such publication bias implies that a review in which only published articles are analysed may be biased towards larger or statistically significant effects or both. This would give rise to erroneous conclusions. It is unlikely that bias of this nature was a factor in the analysis in the present study since all three studies reported that progesterone had no beneficial effect. Many studies that fail to demonstrate a statistically significant result are often left unpublished and the addition of a substantial number of these might alter the combined results. Using the method described by Rosenthal (1979) to estimate the number of such unpublished studies, it was estimated that no additional studies with non-significant findings would have to exist in order to alter the significance of the overall result obtained. Hence, publication bias did not seem to be an important factor in the present study.

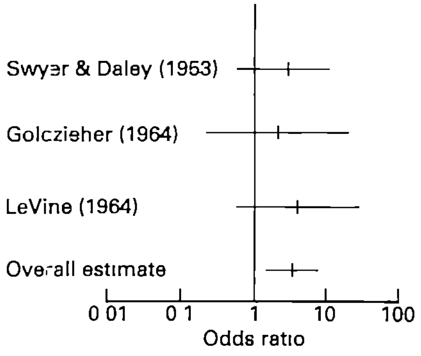

Fig. 1. Efficacy of progesterone in recurrent miscarriage. Odds ratios and their 95% confidence intervals are shown for each of three studies analysed, and for the overall estimate of the treatment effect after statistically combining the results.

Progestational agents have been administered to pregnant patients in an attempt to prevent miscarriage, fetal death and preterm delivery. In some institutions progesterone is frequently used to maintain a pregnancy (Tognoni *et al.* 1980). Also, in a recent survey, one in six general practitioners in England indicated that they still use a progestogen for this purpose (Everett *et al.* 1987). Concern over the safety of synthetic progesterone preparations administered to pregnant women has resulted in complete agreement that these agents should never be used because they may cause masculinization of a female fetus and other teratogenic effects (Wentz 1982). In addition, suppression of the corpus luteum has been demonstrated (Johansson 1971). On the other hand, progesterone and 17-hydroxyprogesterone have not been shown to increase the prevalence of fetal malformation (Katz *et al.* 1985). Also, there is no apparent maternal toxicity from progesterone, as doses of 17-hydroxyprogesterone caproate that are 20–40 times those employed in pregnancy have been used in the treatment of endometrial carcinoma without side-effects (Andrews 1979).

In a meta-analysis, Goldstein *et al.* (1989) found that progesterone and its analogues were ineffective in the maintenance of high-risk pregnancies. However, as shown in the present study, when the analysis is confined to women with recurrent miscarriage, there is support for the suggestion that progesterone may be beneficial in these patients. But before widespread use of progesterone is advocated, the question of its efficacy in women with recurrent miscarriage due to luteal phase defects must be addressed through prospective double-blind randomized controlled trials which must assess the outcome of pregnancy beyond 20 weeks. Such a trial will commence in the near future at McMaster University.

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A randomized controlled trial of the provision of a social support service during pregnancy: the South Manchester Family Worker Project

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Summary. A pilot scheme was introduced in Manchester to provide additional social support to pregnant women at above average risk of giving birth to a low-birthweight baby. The help of lay workers, known as family workers, was made available to eligible women. The effect on infant birthweight of offering the help of a family worker was assessed by a randomized controlled trial. No significant differences were observed between the experimental and control group, but on a number of grounds the interpretation of this finding is not straightforward, and further research is recommended.

The Short Report (House of Commons Social Services Committee 1980) highlighted widespread variations in perinatal health in different areas of the country. Birthweight is acknowledged to be one of the best available indicators of perinatal health (Chalmers 1979) and, by this indicator, the Manchester area compared badly with the country at large. Here, 10·2% of all newborn infants weighed <2500 g, compared with a figure of 7·3% for England and Wales as a whole (Office of Population Censuses and Surveys 1981*a*).

Low birthweight arises as a consequence of preterm onset of labour or retarded fetal growth and is more commonly found among socially disadvantaged women (Office of Population Censuses and Surveys 1981*b*). Psychosocial stress is one possible mechanism by which social disadvantage may give rise to poor pregnancy outcome (Oakley *et al.* 1982; Newton *et al.* 1979; Newton & Hunt 1984). Factors often pointed to are low income, inadequate access to and uptake of services and information, physical effort, isolation, diet, living conditions, ambivalence about the pregnancy and lack of social support (Hart 1971; Papiernik 1984; Spira *et al.* 1981; Wolkind & Zajicek 1981; Brown & Harris 1978; Berkowitz & Kasl 1983; Stein *et al.* 1987).

Whereas it is not possible for health services to reverse the social disadvantage reflected in perinatal statistics, it might be possible to compensate for it by the appropriate redirection of provision. This possibility prompted the institution of the South Manchester Family Worker Scheme, which aimed to provide additional social support for women at above average risk of giving birth to a low-birthweight baby. It was intended that this support would reduce the level of stress, thereby improving the well-being of the pregnant women and ultimately the health of their babies.

The role of the 'family worker' is modelled on that of the *travailleuse familiale* who had been provided as part of the maternal and child health service in the département of Seine-Saint-Denis (Spencer 1982). In Manchester, short-term funding for family workers was obtained from the Manpower Services Commission. Women

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selected for the posts were employed on the basis of personality and general life experience; they had no formal qualifications in the health or social services. The service adopted a client-centred approach, with the tasks of the worker varying according to individual situations. In practice these ranged from providing help with obtaining state benefits, with housing, shopping and other domestic work and childcare, to promoting appropriate use of health and social services and community facilities, and generally acting as confidante (Spencer *et al.* 1987).

The effect of intervention of the workers was assessed in a randomized controlled trial. Since it was designed to assess the potential impact of such a service, randomization took place before knowing which women would eventually accept a family worker. The 'treatment' did not consist in having the assistance of a worker, but in receiving the offer of a family worker.

Subjects and method

The trial took place in two phases: from June 1982 to June 1983 and from June 1984 to September 1985. The year's gap between the two phases was attributable to problems with funding for the family workers. An overview of recruitment and participation in the trial is shown in Fig. 1. Women eligible for the trial were identified following their booking-in visit to either of the two maternity units within the South Manchester Health District. Eligibility was determined according to criteria indicating increased risk of giving birth to a low-birth-weight baby, and was mainly based on national birthweight statistics (Office of Population Censuses and Surveys 1981*b*) and on previous research (Bakketeig *et al.* 1979; Fedrick & Adelstein 1978; Naeye 1979). Any woman satisfying at least two of the entry criteria illustrated by an asterisk in Table 1 was included.

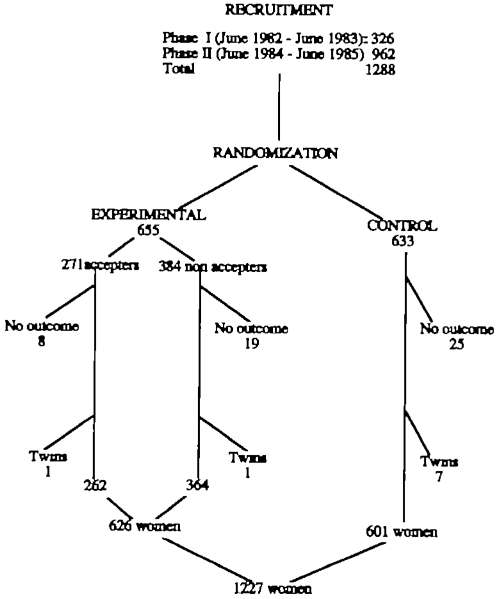

Fig. 1. Overview of trial.

In the second phase of the trial the entry criteria were modified slightly to increase the rate of recruitment. Two new criteria were introduced—'inter-pregnancy interval ≤6 months' and 'parity ≥3'. Existing criteria were in some cases broadened; for example, what was formerly 'previous perinatal death' was extended to 'previous fetal/baby death >12 weeks gestation up to 1 year of life', and 'marital status single' was extended to include known cohabitees. Also, owing to the problems in using the Registrar General's *Classification of Occupations* (Office of Population Censuses and Surveys 1980) to classify women's occupations by social class, the decision was made to categorize certain occupations for women as belonging to social classes IV or V, although they are not officially classified as such (Table 1).

As the family worker was intended to play a preventive role, any women booking in later than 20 weeks gestation were excluded. Intervention began as soon after booking-in as could be arranged. Asian women were excluded from the trial in view of the lower birthweight distribution of these ethnic groups (Kurji & Edouard 1984). Entry to the trial was also confined to those living within the district and pre-defined adjoining areas. During the two periods of recruitment the notes of all women attending the booking-in clinics were screened. In an average month of recruitment those eligible for the trial represented approximately 25% of all women booking in at the two clinics, giving a final total of 1288 women. Allowing for women lost to follow-up and pregnancy loss it was estimated that each group would have approximately 600 subjects; this would give a 76% chance of detecting a difference in mean birthweight of 77 g between the two groups, significant at the 5% level (two-tailed test) assuming a standard deviation of 500 g. (It was estimated that if the intervention was to be clinically of interest a difference in mean birthweight of 77 g between

Table 1. Characteristics of the experimental and control groups with criteria for entry

	Experimental (*n*=655)		Control (*n*=633)	
	Mean (SD)		Mean (SD)	
* Age (years)	23·0 (5·2)		23·2 (5·4)	
Per cent <20 years	45·5%		43·6%	
Weight (kg)	57·2 (10·1) (*n*=643)		57·4 (11·2) (*n*=626)	
Height (m)	1·6 (0·7) (*n*=635)		1·6 (0·7) (*n*=620)	
Body-mass index (kg/m^2)	22·3 (3·6) (*n*=625)		22·6 (4·0) (*n*=613)	
	n	%	*n*	%
*Underweight	247	37	222	35
Parity				
*0	415	63	398	63
1–2	165	25	163	26
*3+	75	12	72	11
Previous low birthweight (<2500g)				
0	587	90	574	91
*1	61	9	52	8
*>1	8	1	8	1
Previous preterm birth (<37 weeks)				
0	605	92	578	91
1	42	6	47	7
>1	8	1	8	1
Previous miscarriage (12–28 weeks)				
0	634	97	610	96
*1	15	2	22	4
*>1	6	1	1	1
Previous perinatal death (28–1 week life)				
0	641	98	614	97
*1	14	2	19	3
*>1	—	—	—	—
Previous neonatal and postnatal deaths (2 weeks–51 weeks life)				
0	640	98	620	98
*1	15	2	12	2
*>1	—	—	1	1
Previous terminations for medical reasons				
0	646	99	619	98
1	9	1	14	2
>1	—	—	—	—
Previous terminations for social reasons				
0	590	90	568	90
1	60	10	59	9
>1	5	1	6	1
*Inter-pregnancy interval <6 months	27	5	24	4
*Single/widowed/divorced/separated	398	61	376	59
*Woman's social class IV or V or unemployed	511	78	477	75
*Partner's social class IV or V or unemployed (% of those with partners only)	216	63	219	62
Diabetic	2	1	1	1
Smoking (cigarettes per day)				
0	326	50	313	49
1–5	69	11	59	9
5–20	247	38	243	39
>20	11	2	14	2

Women's social class IV/V—includes single/widowed/divorced women nursing auxiliaries, shop/sales assistants and hairdressers and *all* unemployed and unclassified women.
Women unemployed—includes housewives and students.
Partner unemployed—includes men in prison, self-employed, students and disabled/sick.
*Entry criteria.

the groups would need to be detected. This value is derived from the difference in mean birthweight between social classes I and II combined and IIIm, IV and V combined.) However, the chance of detecting a decrease in the proportion of low-birthweight babies from 10·2% to 7·3% significant at the 5% level would be <50%.

After recruitment, participants were randomly allocated to the control and experimental groups using random number tables. The experimental group were then sent information describing the scheme and a letter indicating a date and approximate time when the family worker supervisor would call. On her visit the supervisor explained the scheme in more detail, ascertained whether the woman was interested in having a family worker and, if so, which of the workers would be most appropriate. In the first phase the scheme consisted of 10 full-time workers, plus a supervisor and project assistant; and in the second, the equivalent of 20 full-time workers were employed on a full- and part-time basis, plus a supervisor, assistant supervisor and project assistant (although during the last 3 months the staffing was reduced to one-third). On average, a full-time worker would have six clients, each of whom would receive one to two visits per week, although as the service was flexible to the needs of each individual, some received more extensive help than this and others less. Information on birthweight, together with other outcome data on perinatal health, was collected from the women's hospital records. Results have been analysed (*t*- and χ^2-tests) using the SPSS computer package (Nie *et al.* 1975; Hull & Nie 1981).

Results

The population covered by the study is shown in Table 1. As this illustrates, the process of randomization was effective in ensuring comparability between the two groups. A minimum of two criteria was sufficient to qualify for entry to the study, but around two-thirds of those recruited satisfied three or more.

Table 2. Reasons for non-acceptance of help in the experimental group

Reasons for non-acceptance	*n*	%
Not in when visited	91	13·9
No longer/never was pregnant	15	2·3
Moving out of study area	39	6·0
Employed full-time	41	6·3
Not interested	55	8·4
Well supported	143	21·8
Total non-acceptors	384	58·7
Acceptors	271	41·3
Total	655	100·0

Of the women in the intervention group who were eligible for a family worker, 41·4% received help. As shown in Table 2, the remainder of the experimental group could not, or did not, accept the offer of a family worker for a number of reasons, the most common being because enough support was already available.

Of the 1288 women recruited to the trial (Fig. 1) outcome data were unavailable for 52 women (25 in the control and 27 in the experimental group), the most common reason being removal out of the area before childbirth (Table 3). The characteristics of women for whom no outcome was obtained did not differ from those on whom the final analysis was conducted. In addition twins were excluded from the outcome analysis, which was therefore conducted on 1227 women.

Data on mean birthweight and gestation for live- and stillbirths are presented in Table 4. No statistically significant differences were found between the two groups. The experimental group contained a slightly higher proportion (53·1%) of male babies than the control group (47·7%), so that male and female birthweights are presented separately in the tables and figures. Table 5 presents outcome in terms of the proportion of babies in each group who were of low birthweight, the proportion assessed as small-for-gestational-age and those who were born preterm. Small-for-gestational-age was defined as <10th centile on the birthweight-for-gestation charts for males and females published by Milner & Richards (1974). The odds ratios calculated on the proportions and the associated confidence intervals demonstrate the similarity of results obtained from the two groups.

The outcome of all pregnancies in terms of survival is shown in Table 6. The proportions of pregnancies resulting in a livebirth in the control and experimental groups were 96·5% and 95·4% respectively (stillbirth was defined as any baby born dead at or after 28 weeks gestation). Of the livebirths, three babies in the control group and one baby in the experimental group died within the first week, the latter death being due to a lethal congenital malformation. The largest discrepancy in the table is in the number of terminations for social reasons. However, examination of the relation between the stage in the preg-

Table 3. Reasons for unavailability of outcome data in the two groups

Reason outcome information not obtained	Experimental *n*	Experimental %	Control *n*	Control %
Moved	11	1·7	13	2·0
Transferred to hospital outside study area	5	0·8	3	0·5
No trace	3	0·5	3	0·5
Medical record unavailable	1	0·1	0	0·0
Not pregnant	7	1·1	3	0·5
Home delivery	0	0·0	3	0·5
Total	27	4·2	25	4·0

nancy at which these took place and the timing of the visit of the family worker supervisor, did not suggest any connection between the two.

Details on gestational age for all pregnancies, excluding those terminated by induced abortion, are presented in Table 7. There was no evidence to suggest any differences in distribution of gestational length observed in the two groups. (In order to obtain the best estimate of gestational age, the woman's dates were used if she was certain of the date of her last menstrual period. For those who were uncertain, gestational age was based on assessment by ultrasound scan if this was performed before 19 weeks gestation or, where no such reading was available, was taken from the woman's uncertain dates. A comparable proportion of women in the control and experimental group were able to report their dates with certainty.)

As two maternity units were involved in the study, their entry and outcome data were looked at separately to check for any possible discrepancies between the two hospitals. It was found that approximately equal numbers of trial participants had been recruited from each centre, and the profile of the two populations was equivalent both in terms of characteristics at entry to the trial and mean birthweight and length of gestation of the baby.

Discussion

Making available a family worker service for at-risk pregnant women did not significantly influence either the overall mean birthweight or the proportion of low birthweight. The 95% CI for the difference between means did not include the hypothesized 77-g difference in favour of the experimental group. Similarly there was no indication of a selective effect on either preterm birth or fetal growth retardation, or of any other clinically important differences between the two groups.

The size of the study population is perhaps not sufficient for any definite conclusions to be drawn but, bearing in mind the overall structure of the scheme, certain interpretations of the results may be made. One possible inference is that receiving social support from a family worker does not influence the likelihood of giving birth to a low-birthweight baby. Our hypothesis was, however, developed on the basis of substantial previous research (Sokol *et al.* 1980; Olds *et al.* 1980; Larson 1980; Ross & Rutter 1978; Oakley 1985), and our experience

Table 4. Birthweight and length of gestation for all singleton live and stillbirths in the two groups

	Experimental *n*	Experimental mean	Experimental (SD)	Control *n*	Control mean	Control (SD)	Mean difference	*P*	95% CI on difference between means
Birthweight (g)									
All	602*	3179·6	(549·9)	581	3214·5	(553·5)	−34·9	0·3	−97·8 to 28·0
Female	282	3113·3	(511·9)	304	3146·3	(522·4)	−33·0	0·4	−90·5 to 24·5
Male	320	3238·0	(575·8)	277	3289·3	(577·5)	−51·3	0·3	−143·8 to 41·2
Gestational age (days)	603	279·0	(18·7)	581	278·4	(19·1)	0·6	0·6	−1·6 to 2·8

*Birthweight missing for one stillbirth.

Table 5. Proportion of low-birthweight, small-for-gestational-age (SGA) and preterm births in the two groups

	Experimental		Control		Odds ratio	95% CI on odds ratio
	n	%	*n*	%		
Low birthweight (<2500g)						
All births	54*	8·8	50	8·6	1·0	0·7 to 1·6
Livebirths only	52	8·7	49	8·4	1·0	0·7 to 1·6
SGA (<10th centile)†	61	10·0	59	10·2	1·0	0·7 to 1·5
Preterm (<37 weeks)†	60	10·0	54	9·3	1·1	0·7 to 1·6

*Birthweight missing for one stillbirth.
†All births.

in conducting the scheme strongly indicated that family workers increased the subjective well-being of their clients. Perhaps for those women at greatest risk the support of a family worker was not sufficient to counterbalance the adverse factors leading to a low birthweight; or their help was not intensive enough, or, beginning after the first trimester, it came at too late a stage in the process.

Another possibility is that the criteria resulted in the selection of a group inappropriate for the intervention, either because just over half of those offered a family worker did not accept, or because the entry criteria did not adequately target those most likely to benefit.

Women eligible for the trial were not pre-screened to select those more likely to accept a family worker. The non-acceptance rate obtained in practice (58·7%) was higher than anticipated and might partially account for the non-significant findings. We therefore compared women who accepted with those who did not combined with the control group. There was no statistically significant difference between the two groups, although owing to the uneven groupings the chance of detecting a difference was only 52%, and in addition, the groups were not comparable because some criteria were associated with a higher rate of acceptance than others. There tended to be a greater take-up of the service among women who were eligible because they had experience of previous adverse pregnancy outcome, or who qualified under the 'social class IV or V/unemployment' criterion. An analysis of variance to examine the effect of these criteria on eventual birthweight outcome

Table 6. Outcome of pregnancy in the two groups

	Experimental (*n*=626)		Control (*n*=601)	
Outcome of pregnancy	*n*	%	*n*	%
Termination for medical reasons	3	0·5	1	0·2
Termination for social reasons	11	1·8	1	0·2
Miscarriage				
<12 weeks	3	0·5	6	1·0
≥12 weeks	6	1·0	11	1·8
Gestation not known	0	0·0	1	0·2
Stillbirth				
Antepartum	5	0·8	0	0·0
Intrapartum	0	0·0	0	0·0
Gestation not known	1	0·2	1	0·2
Livebirth	597	95·4	580	96·5
Early neonatal death (1–7 days)	1*	0·2	3†	0·5
Late neonatal death (8–28 days)	0	0·0	0	0·0
Survivors at 1 month	596	99·8	577	99·5

*Due to lethal congenital malformation.
†None due to lethal congenital malformation.

Table 7. Distribution of gestational age at birth or miscarriage excluding induced terminations in the two groups

	Experimental		Control	
Gestation (days)	*n*	%	*n*	%
<174	9	1·5	20*	3·3
175–195	2	0·3	1	0·2
196–223	5	0·8	7	1·2
224–258	53	8·7	44	7·4
259–293	456	74·5	443	73·9
294+	87	14·2	84	14·0
Total	612	100·0	599	100·0

* Gestational age was unavailable for one miscarriage For this case gestation was assumed to be <174 days.

showed that the weight of babies born to women who entered the trial on the grounds of previous adverse pregnancy outcome was significantly lower than that of others born in the trial ($P<0{\cdot}001$).

The criteria used resulted in the selection of a population with a rate of low birthweight (8·6%) only marginally higher than that for Manchester as a whole. It may be that the exclusion of Asian women from the trial accounted in part for this, but even so, it does appear that the criteria were not sufficiently stringent to identify those most at risk.

Although psychosocial stress may predispose to the birth of a low-birthweight infant, not all low birthweight is attributable to this cause. Similarly, the risk factors adopted as criteria reflect both collectively and individually a combination of social and medical risk, not all of which could potentially be reduced by social support. This may result in inadequate targeting of those most likely to benefit from the intervention. It may therefore be argued that only certain groups within the overall at-risk population stand to benefit from additional social support. Particular concern is often expressed about the needs of adolescent mothers for example. A subgroup analysis of women less than 20 years old expecting their first child showed a smaller proportion of low birthweight and preterm babies in the experimental group, but because of small numbers the results were statistically inconclusive.

The trial was population based and conducted under conditions similar to those which prevail under non-experimental conditions. For this reason, entry criteria were based on routinely available data from medical records, and no additional prescreening took place. This approach is similar in concept to that of the pragmatic trial described by Schwartz *et al.* (1980). Given the findings of the trial, it is apparent that simply providing a service and targeting it on a quarter of the population, defined as at above average risk according to a mixture of broadly based criteria, will not affect the incidence of low birthweight in that population. We therefore advocate future research to ascertain whether social support through family workers may be effective with closer targeting of those most likely to benefit: using only criteria indicative of stress, social isolation or deprivation and including in the trial only those women both prepared and able to accept the help of a worker. We also recommend that future research include an assessment of maternal well-being in addition to clinical indicators of the baby's health.

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A prospective longitudinal study of social, psychological and obstetric factors in pregnancy: response rates and demographic characteristics of the 8556 respondents

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Summary. This paper introduces the Mater Misericordiae Mothers' Hospital–University of Queensland Study of Pregnancy, a prospective study of 8556 pregnant women interviewed at their first clinic visit, and subsequently interviewed some days after the birth of the baby and again 6 months later. Additional data were derived from the medical record of the pregnancy and delivery. The study was designed to assess the impact of social, psychological and obstetric factors on pregnancy outcome. We present here details of the study design, sampling, response rates and demographic characteristics of the sample.

In recent years improved diagnosis and management of obstetric complications have made a major contribution to the decline in maternal and perinatal mortality and morbidity (Black *et al.* 1982). The development of neonatology emphasizes the impact of technology and intervention on reproductive outcome and there is little doubt that obstetric innovations in the years ahead will further reduce the risks associated with childbirth. The acknowledgment of these obstetric contributions, past and present, is unequivocal. However, there is reason to believe that an ever-decreasing amount of reproductive morbidity will be influenced by purely obstetric or technological innovations.

It is probable that a significant proportion of the remaining obstetric morbidity is related to the social and psychological background and lifestyle of pregnant women. These factors include socio-demographic characteristics of the woman (Dott & Fort 1975; Brennan & Lancashire 1978; Eisner *et al.* 1979; Hendershot 1979; Brooks 1980; Osbourne *et al.* 1981; Robinson *et al.* 1982; Naeye & Peters 1982; Carr-Hill *et al.* 1983; Murphy *et al.* 1984; Ericson *et al.* 1984), her attitude to the pregnancy (Newton & Newton 1962; Heinstein 1967; Pohlman 1969; Laukaran & van den Berg 1980), her mental health state (Gunter 1963; Nuckolls *et al.* 1972; Jones 1978; Standley *et al.* 1979; Newton *et al.* 1979), and such behavioural factors as cigarette smoking (Meyer *et al.* 1976; Rantakallio 1979; Harlap & Shiono 1980), alcohol consumption (Jones *et al.* 1974; Hanson *et al.* 1976; Ouellette *et al.* 1977; Olegsard *et al.* 1979; Harlap & Shiono 1980; Kline *et al.* 1980; English & Bower 1983), analgesic use (Turner & Collins 1975) or the decision to work during pregnancy (Waldron *et al.* 1982; Chamberlain & Garcia 1983; Saurel & Kaminski 1983; Mamelle *et al.* 1984).

Although individual studies have identified many of the factors which might cause obstetric

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Table 1. Public and private births at the Mater Misericordiae Mothers' Hospital (MMH) and in Brisbane, 1981–1984

Year	Patients	MMH *n* (%)	Brisbane *n* (%)	MMH/Brisbane
1981	Public	3827 (61·8)	7012 (48·5)	54·6
	Private	2370 (38·2)	7452 (51·5)	31·8
1982	Public	3836 (57·6)	6667 (43·5)	57·5
	Private	2826 (42·4)	8654 (56·5)	32·7
1983	Public	4185 (59·2)	7190 (46·3)	58·2
	Private	2879 (40·8)	8338 (53·7)	34·5
1984	Public	4319 (65·2)	7047 (47·2)	61·3
	Private	2304 (34·8)	7898 (52·8)	29·2

and perinatal morbidity, there was seen to be a need for a more broadly based study which traced the causal path between socio-demographic factors, attitudes to pregnancy, the woman's mental health and her lifestyle as these interact and contribute to the outcome of the pregnancy. To determine the multifactorial impact of these variables on obstetric outcomes, a prospective longitudinal study was started in Brisbane in 1981.

This paper gives details of the background, selection of patients, methods of sampling, data management, the response rates and demographic and obstetric characteristics of the 8556 participants in the study. It provides a description of the sample to facilitate the interpretation of subsequent papers, and to enable a comparison of the data from this study with that of other studies.

Background

The Mater Misericordiae Mothers' Hospital (MMH) is one of two major obstetric units in Brisbane (estimated population of the Brisbane Statistical Division 1 096 200 at 30 June 1981), and delivers between 6000 and 7000 patients per year, of whom about 60% are public and the remainder are private (Table 1).

Public patients are patients who attend a free hospital clinic for antenatal care and are delivered under the supervision of full-time and visiting medical staff. There is no means testing in Queensland for the use of this facility, and indeed Queensland public hospitals function in a similar manner to British National Health Service hospitals.

Private patients attend obstetricians for antenatal care on a fee-paying basis, are delivered in the hospital, pay room and service fees, and are totally supervised and delivered by their private obstetrician. For most, the fees are largely covered by voluntary health care insurance. The same obstetricians also supervise the care of most of the public patients delivered in this hospital.

Since 1973 the Mater Mothers' Hospital has kept computerized records, containing 191 variables, on all public and private patients. Unfortunately these data did not address the social and psychological factors of potential interest. As a result, a combined project involving interested members of the departments of obstetrics and gynaecology, social and preventive medicine, and anthropology and sociology was started.

Preparation, piloting, validation of questionnaires and logistic details were conducted during 1980. The study proper started on 5 January 1981, and received National Health and Medical Research Council (NHMRC) research funding for 1982–1984 inclusive. This project has now received additional NHMRC funding (1986–1988) for an extension of the original project, to follow up the mothers and the children who are now 5 years of age.

Study details

The study was conducted in the following time sequence.

Phase I. A 117-item questionnaire was provided at the first antenatal visit. This contained a number of scales and questions addressed to the broad areas of marital circumstances, social security benefits, income, housing, employment, education, occupation, migrant status, race, religiosity, drug ingestion, anxiety/depres-

Table 2. Age, marital status and parity by response rate on four occasions when data were collected

	Phase I *n*	Phase II response (%)	Phase III response (%)	Phase IV confined (%)
Age (years)				
≤ 16	196	90	74	94
17–25	5070	87	78	90
26–35	3020	87	83	92
≥36	270	80	76	87
Total	8556			
Variation among groups (*P*)		<0·01	<0·001	<0·05
Marital status				
Single	935	86	70	90
Living together	1005	86	74	89
Married	6183	89	84	92
Other	245	80	71	87
Total	8368			
Variation among groups (*P*)		<0·001	<0·001	<0·01
Family income ($)				
0–10 399	2805	85	75	90
10 400–25 999	4780	90	85	92
≥ 26 000	270	87	84	90
Total	7855			
Variation among groups (*P*)		<0·001	<0·001	<0·01
Previous births, live and still				
Nil	3492	87	79	91
One or more	5064	86	80	91
Total	8556			
Variation between groups		NS	NS	NS

NS, Not significant.

sion, quality of life, subjective/objective stress, pregnancy attitudes/desires and health habits. Most of the demographic data were collected in phase I. The questionnaire was given to the respondent patients by research staff. Any help required to complete the questionnaire due to language or education difficulties was noted.

Phase II. A 103-item questionnaire was given to participants of phase I between the 3rd and the 5th postpartum day. This questionnaire assessed changes which had occurred during pregnancy and also extended into the areas of future family planning, antenatal care, health in pregnancy, social supports, labour and attitudes to the baby.

Phase III. A 103-item mailed questionnaire was completed 6 months after delivery. Apart from a number of items to assess change between the different phases, it particularly examined the areas of social supports, postpartum health, and baby health, development and rearing. Follow-up phone reminders and home visits were used, when necessary, to maximize the response rate.

Phase IV. A 97-item protocol of obstetric data was derived from the hospital records by the study team.

Format of questionnaires

Where possible, use was made of existing or adapted versions of validated scales and indices such as DSSI (Foulds & Bedford 1976*a*, *b*; Bedford & Foulds 1977, 1978; Bedford 1977) to measure neurotic anxiety/depression, and life-style indices from the Alameda study (Belloc & Breslow 1972; Breslow & Enstrom 1980) and marital adjustment developed by Spanier (1976). Standard, shortened and new scales and questions were used only after extensive piloting to assess their reliability and validity.

Data Management

Confidentiality was ensured by using code numbers on all questionnaires, the master code being kept separate and secure.

Returned questionnaires were cleaned, coded, entered and verified on Apple II computers by our research staff. Intermittent transfer of data from floppy disk to University of Queensland PDP 10 computer was performed to provide adequate space for storage and data analysis, and both hard and soft copies were retained for safety in different locations.

The final data file containing the above items plus desired scales and indices for each patient was arranged in 1022 database management system (System 1022 *Users Reference Manual*, 1983 format) and basic analysis conducted using standard SPSS programs (Nie *et al.* 1975). This was later transferred to the IBM computer and SAS system (*SAS User's Guide: Basics* 1985) used for analysis.

The sample

In order to assess the internal and external validity of the study findings, the sampling methods, response rates and sample composition are considered below.

Table 3. Comparison of public and private patients delivered at the MMH (1.1.82 to 31.12.84)

	Public (n=12 029) (%)*	Private (n=8182) (%)*
Age (years)		
≤ 16	2	0·1
17–25	57	24
26–35	38	70
≥ 36	4	6
Marital status		
Single	13	1
Living together	5	0·4
Married	80	98
Other	2	0·6
Medical outcomes		
Gestation ≤ 36 weeks	6·8	5·5
Low birthweight (<1500 g)	1·5	1·1
Low Apgar score at 5 min (≤6)	2·4	2·2
Special care nursery admission	6·7	5·2

* Due to rounding total does not always equal 100

Sampling method and response rates

Data collection began in 1981, according to the following protocol. All public patients seeking obstetric care from this hospital are routinely given an initial appointment for an antenatal clinic visit. Women given such appointments were listed before their attendance and an enrolment questionnaire was prepared for them. Data collection was reduced to all women presenting every second week, for a period, due to resource constraints. At first contact, women were invited to participate in the study. Only 98 (1%) of the 8556 women invited to participate declined the invitation.

Excluded from the study were patients under the care of private obstetricians and patients, often requiring intensive neonatal care, transferred from other hospitals. The response rates for phases I, II and III were respectively 99%, 87% and 81%. The major reasons for the fall in response rates between phases I and II were patients having miscarriages or leaving this area, and between phases II and III (a 6-month period) failure to trace the patient due to change of residence and/or name and lack of a forwarding address. Those lost to follow-up were predominantly young, single, and in the lowest income group, as can be seen when the response rates to each of the three phases were analysed in relation to age and marital status (Table 2). The number of previous births was not related to variations in response rates at each phase.

The sample in relation to public deliveries in Brisbane

Brisbane is a large city in area, divided more-or-less in half by the Brisbane river. The Mater Mothers' Hospital predominantly serves the obstetric needs of women on the south side of the river, while the other major hosptal (The Royal Women's Hospital) provides obstetric services to those on the north side of the river. Table 1 compares the number of births at the Mater Mothers' Hospital with those of similar status (public/private) in Brisbane as a whole during the data collection period. The Mater Mothers' Hospital accounted for between 54·6% and 61·3% of all public patients delivered in Brisbane.

Table 4. Perinatal mortality rates (per 1000 births) for MMH, Brisbane (including MMH), and Queensland (including Brisbane)

	MMH			
Year	Public	Private	Brisbane	Queensland
1981	13·7	12·6	14·4	14·7
1982	9·3	11·9	12·4	13·1
1983	12·4	12·5	12·2	12·6
1984	12·0	14·7	11·0	11·9

Public and private statistics not obtainable for Brisbane or Queensland.

Perinatal deaths include all stillbirths > 20 weeks gestation or ≥ 400 g and neonatal deaths within 28 days of birth.

MMH figures from all deliveries excluding all transfers *in utero* with irretrievable situation.

Sample validity and the exclusion of private patients

This study involved and followed a unique cohort. In its defence it should be noted that many longitudinal studies have used non-representative samples and obtained results which have been found subsequently to reflect associations existing in the broader community. However, the selection of public patients in this study imposes the need for a careful assessment of the extent to which the findings reflect more generally prevalent patterns of association. Limiting the sample to public patients does not, of itself, invalidate the findings which will be reported in subsequent papers, but raises questions about the external validity of the results which can only be addressed using evidence from other studies. Tables 3 and 4 consider in greater detail the comparison between public and private patients with respect to their pregnancies and outcomes.

Table 3 is taken from the hospital records of all deliveries at the Mater Mothers' Hospital over a 3-year period during which most of the data for this study were collected. Public patients tend to be more often concentrated in the youngest age group and to be single. However, there are no major differences in the crude obstetric outcomes between public and private patients (gestation at delivery, birthweight, Apgar score and admission to special care nursery) and perinatal mortality. Perinatal mortality rates for the MMH (public and private), Brisbane and Queensland are compared in Table 4. Interestingly, the perinatal mortality rates for all four comparison groups appear to be similar.

Demographic characteristics of sample

In this paper we limited ourselves to a brief review of some of the salient features of our sample. Subsequent papers will present details of the specific association between the characteristics of our sample and adverse pregnancy outcomes. Although the survey was conducted in a Roman Catholic Maternity Hospital, the participants' stated religious affiliations correspond to those of the total Brisbane population (Table 5) in most respects. Only 14·5% (1211) women claimed to be regular church attenders.

When the partner's occupation is examined (Table 6) it is apparent that this sample is skewed towards the blue collar and manual workers and under-represents professional, administrative and clerical workers, although a broad range of occupations is represented in the sample.

The educational attainments of both the participants and their partners are shown in Table 7 and a close parallel between the two appears evident. Completion of school at 16 and 18 years in Queensland corresponds to the lower and higher leaving certificate examinations elsewhere. Unfortunately the census question relating to education does not permit a direct comparison with the Brisbane population.

The stated family income (Table 8) reflects the lower socio-economic status of the survey group. Only 3·4% of respondents report an income of $26 000 or more (compared with 19% for Brisbane as a whole).

A relatively high proportion, 41·7% (3464), either owned or were in the process of buying their house, while 40·7% were renting and a further 14·5% were living with relatives or

Table 5. Religious affiliation of respondents and women in Brisbane

Religious affiliation	Respondent (n=8556) (%)*	Brisbane (n=352 093) (%)
Roman Catholic	28	27
Anglican	30	26
Other Christian	22	26
Non-Christian	1	12
No religion	14	9
Not stated	6	–

* Due to rounding total does not equal 100.

Table 6. Occupation of partners of respondents and men in Brisbane

Occupation	Census codes	Partner (*n*=8556) (%)	Brisbane (*n*=188 996) (%)
Professional, administrative	(0,1)	11	22
Clerical	(2)	5	12
Sales	(3)	5	8
Farmers, fishermen	(4)	2	1
Miners, transport, communication	(5,6)	9	7
Tradesmen, process worker	(7,8)	52	38
Service, sport, armed services	(9,10)	5	8
Unknown, inadequately described		11	4

parents. The remainder lived in caravans, hostels, etc., and of the whole group 12·1% reported they were experiencing some difficulty with accommodation. The racial origins of the survey group were predominantly white—91·8% (7511), with 3·7% (305) Asian, 1·8% (149) Maori and Islanders, and 2·3% (188) Australian Aborigines. A further 0·7% (48) of women reported a mixed racial background. The age distribution of the 8556 patients who participated in the survey and their partners is shown in Table 9.

Of the total survey cohort of 8556 patients, 2789 (32·6%) were primigravidae. The past obstetric history of the remaining 5767 included 12 161 previous pregnancies, of which 2276 (18·2%) ended in miscarriage before 20 completed weeks gestation, 739 (5·1%) were reported to have been terminated, and 59 (0·5%) were ectopic pregnancies. The 9087 previous pregnancies which continued after 20 weeks resulted in 9149 babies, which included 60 sets of twins and one set of triplets. There were 133 stillbirths, 116 neonatal deaths (day 1–28 after delivery), and a further 78 died during infancy or childhood.

Lifestyle characteristics

Only 43·3% of the participants stated that they had planned to become pregnant, 10.4% were unsure, and 46·3% had not planned this pregnancy. In a corroborative question only 49·3% of women stated that they had 'wanted to get pregnant'. Details of the socio-demographic characteristics of women having unplanned pregnancies have already appeared (Najman *et al.* 1984). In relation to health habits, 51·1% of women reported smoking before the pregnancy and 40·1% had smoked in the week before the first clinic contact. Some 9·5% of women reported smoking 20 or more cigarettes a day. Alcohol use before conception was reported by 74·5% of the sample and by 49·6% after conception. Only a small percentage (4·0%) reported alcohol use a few times a week or more, early in pregnancy. A significant percentage (17·3%) of women claimed to have used marijuana before the pregnancy and 3·1% reported marijuana use early in pregnancy.

Discussion

A number of social and psychological factors have been associated with poor obstetric outcome. Outstanding are the observations by Baird (1973) in relation to social class. Social class itself is an abstract concept based on a variety of subfactors as described by Najman *et al.* (1979), and Siskind *et al.* (1987), Jones (1978) and Newton *et al.* (1979) have noted associations between stress and labour complications and preterm delivery respectively, although the effects of stress on health and obstetric outcome

Table 7. Education of respondents and their partners

Education	Respondent (*n*=8556) (%)	Partner (*n*=8556) (%)
No school or		
opportunity school	1	1
Primary school	4	4
Started secondary school	14	12
Left school		
15–16 years	53	45
17–18 years	9	12
College, trades, etc	14	14
University	3	4
Other/unknown	2	8

Table 8. Comparison of family/household incomes of respondents and Brisbane residents (for approximately similar income categories)

Family income of respondents ($)	(*n*=8556) (%)	Household income of Brisbane residents ($)	(*n*=233 324) (%)
0–10 399	33	0–10 000	28
10 400–25 999	56	10 001–26 000	46
≥26 000	3	≥26 001	19
Unknown	8	Unknown	7

can apparently be reduced by strong social supports (Nuckolls *et al.* 1972).

Various behavioural problems, such as failure to obtain adequate antenatal care (Keeping *et al.* 1980), cigarette smoking, excessive alcohol consumption, work in the third trimester and contact with or ingestion of a wide variety of chemicals (Hill & Stern 1979) have also correlated with less favourable obstetric outcome.

While these findings from previous studies are of interest and of clinical importance in defining risk factors in pregnancy, they fail to demonstrate the path by which there is an effect on obstetric morbidity and mortality.

We have specifically embarked on a broadly based longitudinal study and accept that we have had to abandon some depth in certain areas in order to cover a wider range of factors but suggest this is a necessary compromise.

It is also relevant to note the diminished response rate with each phase (although this is expected in such surveys) as the main loss especially in phase III is due to untraceable change of domicile and/or name. Another concern is the relative infrequency of some outcomes (e.g. perinatal death), although the large sample size and the frequency of other outcomes (e.g. preterm delivery, low birthweight) provides adequate numbers of cases for the purpose of comparison.

The demographic and obstetric characteristics we have described for our study group are not only necessary for accurate comparisons but underline the range of variables which have to be considered in the eventual analysis to determine the proper weighting to be assigned to social, psychological, behavioural and obstetric factors as these influence obstetric outcomes.

Table 9. Age of respondent and partner

Age (years)	Respondent (*n*=8556) (%)*	Partner (*n*=8556) (%)*
≤16	2	0·1
17–25	59	37
26–35	35	45
≥36	3	10
Unknown		8

* Due to rounding totals do not equal 100

Conclusion

In recent years there has been considerable interest in the extent to which the social environment, lifestyle and mental health can influence the outcome of pregnancies. In contrast to the established and sophisticated research efforts aimed at identifying the pathological basis of obstetric morbidity, we find that much research which has investigated the social and behavioural environment of the mother and child has provided important insights but left many questions unanswered. The results of many previous studies, largely focusing on single factors, need to be amalgamated by identifying the independent contributions and interaction of a wide range of social, psychological and obstetric factors in pregnancy outcomes. We are directing our efforts to this end for our sample of Brisbane women. This initial paper details the characteristics of our sample to enable other researchers to assess the more general relevance of our results which will appear in a series of subsequent papers.

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Socio-economic status and pregnancy outcome. An Australian study

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Summary. A prospective cohort of 8556 pregnant women attending the Mater Misericordiae Mothers' Hospital in Brisbane was examined to consider the impact of socio-economic status on pregnancy outcome. The indicators of socio-economic status selected were family income, maternal education and paternal occupational status. Pregnancy outcomes considered were preterm delivery, low birthweight, low birthweight for gestational age, and perinatal death. Subsidiary analyses were also undertaken for Apgar scores, time to establish respiration, need for mechanical respiration and admission to intensive care. Before adjustment, the main consistent association was between the occupational status of the father and three measures of perinatal morbidity. Initial adjustment for the mother's socio-demographic background and weight/height ratio reduced the strength and statistical significance of the above associations, while further adjustment for lifestyle variations between the three status groups further reduced the above associations to marginal statistical significance. The findings suggest that observed class differences in pregnancy outcome are attributable to the mother's personal characteristics (height/weight^2, parity) and her lifestyle.

The relation between socio-economic status and perinatal mortality was brought into focus by Baird & Wyper (1941) when they stated 'there is a large wastage of child life associated with childbirth in Scotland, intimately connected with unfavourable economic conditions, and malnutrition and fatigue of the mother'.

Baird (1945, 1973) analysed perinatal mortality against social class (using the Registrar General's classification) and confirmed the existence of an inverse association between stillbirth and neonatal death rates and social class. Since then, a number of European, British and American studies have replicated these observations, which are well summarized by Antonovsky & Bernstein (1977) and Gray (1982).

Illsley (1983) noted that, while perinatal mortality had decreased dramatically between 1951 and 1977 in Scotland, the mortality ratio between the various social classes had remained virtually unchanged, a point confirmed more recently by Whitehead (1987) for Britain in general.

The evidence available to date demonstrates that class differences are predictors of pregnancy outcome for a number of countries, but leaves three key questions unanswered. Firstly, there is some uncertainty concerning the extent of class

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variations in pregnancy outcome in Australian obstetric practice. This is, in part, derived from the general belief that there has been a unique pattern of Australian migration (early convict origins, then a large number of displaced persons following World War II) coupled with a widely held egalitarian ethic and the lack of an 'inherited' class structure. Secondly, as class itself cannot logically 'cause' particular outcomes of pregnancy (since class is a concept, an abstraction for research purposes), there is a need to determine the relevant causal sequence. Thirdly, and more specifically, while class may be correlated with pregnancy outcome, it is not clear whether such an association is a consequence of specific behavioural differences or the result of a general process associated with chronic economic disadvantage.

The studies of Dasvarma (1980), who found an association between neonatal mortality rates and Aboriginal and ex-nuptial births, and Johnston (1980), who showed an inverse relation between perinatal mortality and maternal education in two Hobart suburbs, provide indirect evidence that some associations between class and pregnancy outcome may be present in Australia. However, while Lumley *et al.* (1985) found an inverse association between low birthweight and social class in Tasmania, this association did not extend to the group at greatest risk, those children born with a birthweight below 1500 g. Siskind *et al.* (1987) have shown that lower class areas of Brisbane have higher infant mortality rates, but Australian data for a cohort observed longitudinally have not been available.

The purpose of this paper is to consider social class/socio-economic status differences in pregnancy outcome in a large hospital-based Brisbane sample.

Subjects and methods

Sampling and research design

A prospective cohort of 8556 patients attending the Mater Misericordiae Mothers' Hospital in Brisbane was enrolled in the study between 1981 and 1983. Full profiles of their demographic, social, cultural and past obstetric characteristics have been detailed by Keeping *et al.* (1989). Data for this paper were obtained from phase I (a questionnaire administered at the first clinic visit) and phase IV (the medical record of the pregnancy and its outcome).

Full details of data collection have been reported previously (Keeping *et al.* 1989). The data were analysed using SAS (*SAS User's Guide: Statistics* 1985) on an IBM mainframe computer at the University of Queensland. The analysis involved the use of the program CATMOD which provides odds ratios of particular outcomes adjusted for a range of potential confounders.

The analysis aimed to establish the relation between social class/socio-economic status and the outcome of pregnancy, and the influence of associated variables.

Social class/socio-economic status

Social class, despite its abstract status, is, according to Illsley (1983), an effective epidemiological concept based on the recognition that paternal occupation is a sensitive indicator, not only of working conditions, but also of income, education, housing, diet and a variety of social, economic and cultural characteristics which are often loosely described as 'lifestyle'. While Illsley has correctly noted that the variable 'class' provides indirect evidence of the association between the social circumstances of groups in the community and their health, it remains unclear why such an association exists. Two types of possibility may be considered in the above context. Firstly, class differences may influence a limited number of specific lifestyle variables which, in turn, modify the mothers' health and the outcome of pregnancy. Secondly, class differences may be associated with such a wide variety of lifestyle factors and socio-environmental differences that it may be more appropriate to conceptualize these under a more general schema (see Syme & Berkman 1976; Syme 1986; Najman 1980; Marmot *et al.* 1984). According to this latter view, class differences in health are attributable to a constellation of interacting variables which are unique to particular class groups. The impact of this constellation of factors, it is argued, renders lower class groups more 'susceptible' to a wide range of diseases and causes of death. Until these variables and their mode of expression are better known, the concept 'class' might best be treated, according to this latter view, as an identifying label which directs attention to an area of concern.

While mortality differences have been repeatedly demonstrated in the relatively stratified British (and the more general European) class structure, there are many difficulties in transposing this observation to the Australian situation. Differences in racial, social and cultural background, population mobility (both in housing and employment), changes in wage, employment and educational structure, a low population density, and often a marked disparity between income and occupational status, as well as an inappropriately conceptualized Australian Bureau of Statistics' classification (Najman 1988) have created difficulties in determining a clearly defined class structure in Australia.

For these reasons, sociologists and epidemiologists in Australia, such as Najman *et al.* (1979) and McMichael (1985), have tended to use more specific indices such as occupational status, income and education as indicators of social class, rather than occupation as defined by the British Registrars General.

Following this practice we have chosen to use three somewhat distinct indicators of socio-economic status, namely:

Family income. This was used because it is likely to reflect the mother's and father's combined economic position relative to other families. Income inequalities are likely to distinguish most directly between families' capacities to purchase goods (food, clothing, etc.) and services (transport, communication, support facilities when unwell). Such a variable elevates the position of dual-income families relative to indicators based upon the circumstances of one or other of the partners. Respondents were provided with seven categories of income in the questionnaire and asked to indicate which category was closest to their family gross income. These have been reduced to five, with the lowest income group receiving well below the minimum wage.

Mothers' education. This was used to provide a more direct measure of the woman's relative socio-economic status. Numerous studies in developing countries have shown that more educated women have lower perinatal mortality rates. Higher education not only presumes higher economic standing but suggests a more informed approach to both self care and the use of the health care system. Better knowledge of health-related behaviours is also likely to be reflected by the woman's education level. For analysis the seven alternatives provided to respondents were amalgamated into four categories. Included in the college group are women with varied non-university tertiary qualifications (e.g. secretarial). The recoded version of the variable is perhaps best interpreted as a nominal scale.

Fathers' occupational status. This was used because conventional families are generally ranked according to the relative standing of the main income earner, usually the male head-of-house. Occupations were allocated to status scores according to the scale originally developed by Congalton (1969) and updated by Daniel (1983). According to this scale occupations are ranked on the criterion of 'status' using predetermined community norms for each occupation. Typically, medical practitioners, other professionals and directors of major companies are perceived to have high prestige, while cleaners, refuse collectors and labourers receive a low ranking. For the purpose of categorical comparison these rankings were recoded into three ordered groups.

Table 1 provides a correlation matrix of the three SES indicators as well as the mother's age and parity. All the variables are significantly correlated, though the correlations are not strong. The relatively weak intercorrelation between the SES indicators reflects, in part, the choice of the three somewhat distinct measures used. Previous studies in Australia (Broom *et al.* 1968) and Israel (Abramson *et al.* 1982) point to correlations between indicators of perhaps twice

Table 1. The correlation of selected socio-demographic variables in a sample of pregnant women in Brisbane (Kendall's Tau-B)

	Family income	Mothers' education	Fathers' status
Mothers' education	0·16**	—	—
Fathers' status	0·22**	0·16**	—
Mothers' age	0·13**	−0·03*	0·10**
Parity	0·10**	−0·09**	0·02*

**$P<0{\cdot}01$; *$0{\cdot}01>P>0{\cdot}05$.

those observed in Table 1, if the male partners' characteristics are correlated, rather than the characteristics of either (maternal education, paternal occupation) or both (family income) partners, as is the case in this study.

Pregnancy outcome

Traditionally, perinatal mortality has been used to judge the effect of social class/socio-economic status on pregnancy outcome. However, the decline in perinatal mortality over the past decades has made this outcome a relatively rare event. Much of the residual mortality is due to lethal malformations and very preterm delivery, and may not be of use with a sample of modest size. We have therefore also selected a range of pregnancy outcomes which reflect perinatal morbidity and which are likely to identify those who are at higher risk of perinatal death.

The selected outcomes used are: (i) preterm delivery (≤36 completed weeks gestation); (ii) low birthweight (<2500 g); (iii) birthweight <5th centile for gestation (based on hospital birthweight data); (iv) perinatal mortality (includes all stillbirths >20 weeks gestation or ≥400 g and neonatal deaths within 28 days of birth).

Results

The three indicators of socio-economic status (SES) are correlated with a number of lifestyle variables including diet, levels of passive recreation (TV watching), cigarette use and missed antenatal visits (Table 2). In each instance the women who score higher on the SES indicator report an apparently healthier lifestyle, smoking fewer cigarettes, being more consistent attenders for antenatal care, eating breakfast more regularly, and watching less television. The above lifestyle differences, it should be stressed, are a partial list of what are more general SES behavioural variations within our sample.

Each of the above associations has been reported because it is apparently related to the outcome of the pregnancy (Table 3). This is also the case for some socio-demographic and physical characteristics of the mother as indicated in Table 3. This Table provides a clear indication that associations between pregnancy outcome and SES may be a function of the socio-demographic, physical and lifestyle variables listed in Table 2. These include the findings that the youngest women and nulliparous women have lower birthweight and more low-weight-for-gestation babies; that more obese women have heavier babies; that women who rarely eat breakfast have lower birthweight babies; and that women watching more television or smoking have more low birthweight and low-birthweight-for-gestation babies.

Table 4 shows that there is a consistent association between preterm delivery and the mothers' SES ratings as indexed by the fathers' occupational status. This association reduces to marginal statistical significance when differences are adjusted for lifestyle and relevant socio-demographic and physical variables. There is no association between the preterm delivery rate and the other two indicators of socio-economic status.

A similar finding appears in Table 5 when we examine the association between low birthweight and SES. Women who fall into the lowest status group appear to manifest consistently the highest rate of low birthweight. These differences remain statistically significant after adjustment for the mothers' age, parity, marital status and weight/height, but diminish to marginal statistical significance (for occupational status) or non-significance (for mothers' education)

Table 2. The association between lifestyle and socio-economic status in a sample of pregnant women in Brisbane (Kendall's Tau-B)

	Family income	Mothers' education	Fathers' status
Cigarettes			
First visit	0·08**	0·09**	0·07**
Before birth	0·08**	0·09**	0·07**
Missed antenatal visits	0·07**	0·06**	0·07**
Breakfast regularly	0·05**	0·06**	0·05**
Hours television per day	0·03*	0·09**	0·05**

**P<0·01; *0·01>P>0·05.

Table 3. Mothers' social background, lifestyle and the outcome of pregnancy (Pearson correlation)

	Birthweight	Gestation at delivery	Birthweight/gestation
Social background			
Mothers' age	0·08*	−0·05*	0·10*
Number of live children	0·11*	0·00	0·13*
Mothers' height/weight ratio	0·10*	0·02	0·10*
Lifestyle			
Cigarettes			
First visit	−0·19*	−0·07*	−0·18*
Before birth	−0·19*	−0·05*	−0·19*
Missed antenatal visits	0·00	0·03*	0·02
Breakfast regularly	0·09*	0·02	0·10*
Hours television per day	−0·04*	−0·02	−0·04*

*$P<0{\cdot}01$.

once there is further adjustment for the mothers' lifestyle.

This latter pattern is evident again in Table 6 where family income and fathers' occupational status are associated with low-weight-for-gestation, but adjustment in successive stages for the mothers' socio-demographic and physical characteristics reduces the significance of these associations, and for lifestyle the associations become of marginal significance (for family income) or non-significant (for occupational status).

Table 7 indicates that, despite some trends in the expected direction, there is no association between perinatal mortality and SES in our sample. While not statistically significant, the

Table 4. Socio-economic status by preterm delivery (≤36 completed weeks)

	Rate/100 births	Odds ratio unadjusted	Odds ratio adjustment 1*	Odds ratio adjustment 2†
Family income ($)				
0– 5199	6·4 (547)	1·38	1·03	0·98
5200–10 399	4·6 (1964)	0·97	0·87	0·83
10 400–15 599	4·5 (2683)	0·95	0·94	0·93
15 600–20 799	5·1 (1188)	1·09	1·09	1·09
20 800+	4·7 (764)	1·00	1·00	1·00
		$\chi_4^2=4{\cdot}2$	$\chi_4^2=2{\cdot}0$	$\chi_4^2=2{\cdot}8$
		$P=0{\cdot}38$	$P=0{\cdot}74$	$P=0{\cdot}60$
Fathers' occupational status				
Very low	6·3 (1200)	1·72 (1·2–2·4)‡	1·59 (1·1–2·3)	1·50 (1·1–2·1)
Low-middle	4·8 (4038)	1·30 (1·0–1·7)	1·23	1·17
Middle-upper	3·7 (1684)	1·00	1·00	1·00
		$\chi_2^2=9{\cdot}5$	$\chi_2^2=6{\cdot}8$	$\chi_2^2=5{\cdot}3$
		$P=0{\cdot}009$	$P=0{\cdot}03$	$P=0{\cdot}07$
Mothers' education				
Incomplete grade 10	6·1 (1433)	1·33	1·15	1·05
Complete grade 10	4·8 (4127)	1·02	0·94	0·91
Grade 12 and/or university	4·3 (921)	0·92	0·90	0·93
College	4·7 (1130)	1·00	1·00	1·00
		$\chi_3^2=5{\cdot}4$	$\chi_3^2=2{\cdot}4$	$\chi_3^2=1{\cdot}19$
		$P=0{\cdot}14$	$P=0{\cdot}50$	$P=0{\cdot}76$

*Adjustment 1 for age, parity, marital status and mothers' weight/height^2.
†Adjustment 2 for the above plus smoking and eating breakfast regularly.
‡95% confidence intervals (CI) for odds ratios.

Table 5. Socio-economic status by low birthweight ($\leqslant$2499g)

	Rate/100 births	Odds ratio unadjusted	Odds ratio adjustment 1*	Odds ratio adjustment 2†
Family income ($)				
0– 5199	6·8 (546)	1·51 (0·9–2·5)‡	1·30	1·25
5200–10 399	5·4 (1964)	1·18	1·13	1·05
10 400–15 599	5·1 (2683)	1·13	1·16	1·14
15 600–20 799	4·6 (1188)	0·99	0·98	0·99
20 800+	4·6 (764)	1·00	1·00	1·00
		χ_4^2=4·5	χ_4^2=1·98	χ_4^2=1·53
		P=0·35	P=0·74	P=0·82
Fathers' occupational status				
Very low	6·5 (1200)	1·70 (1·2–2·4)	1·69 (1·2–2·4)	1·53 (1·1–2·2)
Low-middle	5·5 (4038)	1·43 (1·1–1·9)	1·40 (1·1–1·9)	1·29 (0·9–1·7)
Middle-upper	3·9 (1684)	1·00	1·00	1·00
		χ_2^2=10·0	χ_2^2=9·0	χ_2^2=5·8
		P=0·007	P=0·01	P=0·06
Mothers' education				
Incomplete grade 10	7·0 (1433)	1·56 (1·1–2·2)	1·48 (1·0–2·1)	1·25
Complete grade 10	5·1 (4126)	1·12	1·10	1·02
Grade 12 and/or university	4·5 (921)	0·97	0·97	1·02
College	4·6 (1130)	1·00	1·00	1·00
		χ_3^2=10·6	χ_3^2=7·6	χ_3^2=2·8
		P=0·01	P=0·05	P=0·43

*Adjustment 1 for age, parity, marital status and mothers' weight/height^2.
†Adjustment 2 for the above plus smoking and eating breakfast regularly.
‡95% CI for odds ratios.

lowest SES group, in every instance, manifests the highest (unadjusted) mortality rates. This, of course, reflects the low number of deaths in this sample, and, in view of the earlier findings, should not be interpreted as evidence inconsistent with that derived from Tables 4–6. In a second set of analyses, data were processed using the analysis of variance program in the general linear model (GLM) producing similar results to those in Tables 4–6. Regardless of whether the analysis involved a comparison of adjusted mean differences or adjusted odds of particular outcomes (equivalent to relative risks), the findings point to some modest associations which diminish to marginal statistical significance once lifestyle adjustments are added to those relating to the physical characteristics of the mother.

The categorical analysis was also repeated for a range of additional indicators of pregnancy outcome. These included low Apgar scores at 5 min ($\leqslant$6), time to establish respiration $\geqslant$3 min, baby requiring mechanical respiration and admission to the intensive care nursery for $\geqslant$15 days. These failed to produce statistically significant (unadjusted) associations with the three SES indicators used in this study.

Discussion

The results suggest that, in this community, low socio-economic status as measured by the fathers' occupational status, is associated with a number of indicators of perinatal morbidity. Adjustment for the mothers' age, parity, marital status and weight/height reduces the magnitude and significance of the above differences as does further adjustment for indicators of the mothers' lifestyle.

Two reservations may be raised in the context of these findings. The first is that the database may not be sufficiently large to reveal statistically significant associations. This would appear unlikely as our sample is half the size of that of the 1970 British Birth Cohort (Chamberlain *et al.* 1975) but, by contrast, our data have the advantages of including detailed social and obstetric data.

The second reservation is that our sample is under-represented in the upper socio-economic group. A comparison of perinatal mortality rates

Table 6. Socio-economic status by babies born small for gestational age*

	Rate/100 births	Odds ratio unadjusted	Odds ratio adjustment 1†	Odds ratio adjustment 2‡
Family income ($)				
0– 5199	6·4 (546)	2·02 (1·2–3·4)§	1·99 (1·1–3·5)	1·95 (1·1–3·4)
5200–10 399	5·8 (1964)	1·82 (1·2–2·8)	1·82 (1·2–2·9)	1·67 (1·1–2·6)
10 400–15 599	4·4 (2583)	1·35	1·45 (0·9–2·3)	1·42
15 600–20 799	4·0 (1188)	1·22	1·21	1·20
20 800+	3·3 (764)	1·00	1·00	1·00
		χ^2_4=14·2	χ^2_4=11·0	χ^2_4=8·4
		P=0·007	P=0·03	P=0·079
Fathers' occupational status				
Very low	5·2 (1200)	1·47 (1·0–2·1)	1·43 (1·0–2·1)	1·27
Low-middle	5·0 (4038)	1·41 (1·1–1·9)	1·36 (1·0–1·8)	1·23
Middle-upper	3·6 (1684)	1·00	1·00	1·00
		χ^2_2=6·1	χ^2_2=4·7	χ^2_2=2·1
		P=0·05	P=0·09	P=0·36
Mothers' education				
Incomplete grade 10	5·7 (1433)	1·28	1·35	1·11
Complete grade 10	4·8 (4126)	1·06	1·07	0·95
Grade 12 and/or university	4·0 (921)	0·89	0·94	1·04
College	4·5 (1130)	1·00	1·00	1·00
		χ^2_3=4·10	χ^2_3=4·4	χ^2_3=1·18
		P=0·25	P=0·22	P=0·76

*Defined as the bottom 5% of weight for gestation.
†Adjustment 1 for age, parity, marital status and mothers' weight/height^2.
‡Adjustment 2 for the above plus smoking and eating breakfast regularly.
§95% CI for odds ratios

for public and private patients at the Mater Hospital showed no differences once transfers from other hospitals were excluded from the calculations (Keeping *et al.* 1989). Whitehead (1987), in her review of the British and other literature, notes that studies which have been limited to a cohort which is relatively homogeneous (e.g. the Whitehall study—Marmot *et al.* 1984) have observed differences between socio-economic strata which are even greater than those observed in a broader population, perhaps in part because more reliable and valid occupational data are obtained. Further, we would argue that we have sufficient spread, from middle to lower class, to identify substantial differences if they existed. Moreover, from a practical point of view, any effective intervention programmes would be directed to reducing the socio-economic gap between the low to middle levels, and these groups are well represented in our sample.

Three issues, identified in the introduction, are of relevance in this discussion. Firstly, the data from this study point to socio-economic differences in perinatal morbidity with mothers in the lowest status category manifesting significantly higher rates of preterm delivery, low birthweight and low birthweight for gestational age. This finding is consistent (and interestingly of a similar magnitude) with the results reported by Lumley *et al.* (1985) for Tasmanian infants born between 1975 and 1983, though their classification of SES differs markedly from ours. While we have not found an association between perinatal mortality and SES, Siskind *et al.* (1987) do report such an association for a Brisbane area-based study. The small numbers of deaths in our sample suggest that the failure to observe an association between SES and perinatal mortality should not be considered evidence denying the existence of such an association. When we compare the adjusted point estimates of the magnitude of elevated risk manifested by the lowest SES group, we observe about a 50% increased rate of adverse outcomes in the lowest group in this study and those by Lumley *et al.* (1985) and Siskind *et al.* (1987).

The second issue of concern relates to the

Table 7. Socio-economic status by perinatal mortality

	Rate/1000 births	Odds ratio unadjusted	Odds ratio adjustment 1*	Odds ratio adjustment 2†
Family income ($)				
0– 5199	16·5 (546)	1·41	1·22	1·15
5200–10 399	11·7 (1964)	0·99	0·88	0·83
10 400–15 599	7·1 (2682)	0·60	0·60	0·58
15 600–20 799	12·6 (1187)	1·08	1·01	1·00
20 800+	11·8 (764)	1·00	1·00	1·00
		χ^2_4=5·63	χ^2_4=3·74	χ^2_4=3·83
		P=0·23	*P*=0·44	*P*=0·43
Fathers' occupational status				
Very low	14·2 (1198)	1·27	1·12	1·04
Low-middle	8·9 (4037)	0·79	0·74	0·71
Middle-upper	11·3 (1684)	1·00	1·00	1·00
		χ^2_2=2·62	χ^2_2=2·20	χ^2_2=2·27
		P=0·27	*P*=0·33	*P*=0·32
Mothers' education				
Incomplete grade 10	14·0 (1432)	1·14	0·97	0·88
Complete grade 10	9·0 (4126)	0·72	0·70	0·65
Grade 12 and/or university	13·1 (919)	1·05	0·96	0·99
College	12·4 (1131)	1·00	1·00	1·00
		χ^2_3=3·26	χ^2_3=2·14	χ^2_3=2·67
		P=0·35	*P*=0·54	*P*=0·45

*Adjustment 1 for age, parity, marital status and mothers' weight/height^2.
†Adjustment 2 for the above plus smoking and eating breakfast regularly.

causal sequence associating SES and perinatal morbidity. The data from this sample suggest that a component of the SES effect is attributable to the mother's age, parity, marital status and weight/height ratio. Yet a further component of this association is attributable to some specific lifestyle differences. Thus it seems that women in the lowest status group have more adverse pregnancy outcomes because they are younger, less often married, and of lower parity, as well as more often being smokers and eating breakfast less frequently.

This leads to the third and related point, that adjustment for all the above variables reduces the observed association between SES and perinatal morbidity to one of marginal statistical significance, suggesting that SES differences in perinatal morbidity are attributable to a relatively small number of characteristics of the mother, only some of which represent modifiable behaviours. While bearing in mind the limitations of the sample enrolled in this study, our findings appear to differ from those reported elsewhere.

Marmot *et al.* (1984) have, in the context of the Whitehall Study, argued that class differences in adult mortality remain even after the data are adjusted for lifestyle variations between the classes. A similar finding was reported in data from the Alameda County Study, California, when it was observed that SES differences remained even after adjustment for 13 known risk factors (Berkman & Breslow 1983). Slater *et al.* (1985) have also found, for a large American sample, that self-rated health varies with various indices of SES even after adjustment for the respondent's age and health habits. They suggest that SES makes an 'independent' contribution to health status. Whitehead (1987), in a comprehensive review of the UK and international literature regarding SES differences in mortality, points out that class differences may be observed in nutrition, housing, exercise patterns, cigarette smoking, alcohol use and presumably a wide range of other potentially health pertinent behaviours. Illsley (1986) has further argued that a component of the class difference in mortality is attributable to a process of social mobility, with women who are more likely to have adverse pregnancy outcomes (they are shorter, score lower on IQ tests) being downwardly mobile. The contribution of this biological component to the socio-economic difference in pregnancy outcomes is likely to be modest (Wilkinson 1986).

Thus the data we have reported disagree with the existing literature in a number of respects. Our study points to some socio-economic differences in pregnancy outcomes, though these are of a comparatively modest magnitude. A component of this difference appears to be attributable to the socio-demographic and physical characteristics of the mother and a second component to a small number of lifestyle factors.

Our data may be interpreted in various ways. Epidemiologists and sociologists might argue that there remains a residual effect of marginal significance after allowing for the effects of such variables as age, parity, marital status, smoking and eating breakfast regularly. Indeed, it could be argued that the very existence of an association between indicators of socio-economic status and the outcome of pregnancy (regardless of whether the association is mediated by the mother's lifestyle) demands that methods of reducing the level of socio-economic inequality should be identified, and that lifestyle intervention programmes (e.g. to reduce cigarette smoking by pregnant women) be mounted.

A second, more pragmatic, interpretation could be advanced by the practising obstetrician who might argue that low socio-economic status is not an independent cause of perinatal mortality or any of the more serious indicators of perinatal morbidity. Obstetricians might wish to question whether the birthweight difference was of sufficient magnitude to be of obstetric importance.

We have previously partitioned birthweight in our population (Keeping *et al.* 1979) and considered the effect of many factors—maternal age, patient status, height and height-adjusted weight, country of origin, individual family and sex of infant—and conclude that the differences in mean birthweight due to socio-economic influences in our area are of no real independent obstetric significance. However, socio-economic status is clearly associated with 'lifestyle' differences which are both obstetrically significant and an appropriate focus of obstetric intervention.

Conclusions

Low socio-economic status appears to have a modest impact on pregnancy outcome in a public hospital sample of Australian obstetric patients. In this sample, provided allowance is made for age, parity, smoking and alcohol consumption, then low socio-economic status should not be regarded as an independent risk indicator in pregnancy but rather as primarily associated with the physical characteristics of the mother and her lifestyle. Women of lower socio-economic status engage in higher rates of unhealthy behaviours. These behaviours and the circumstances which lead to their continuation should continue to be the focus of obstetric attention.

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Unemployment and reproductive outcome. An Australian study

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Summary. The Mater–University of Queensland Study involves the follow-up of 8556 pregnant women who were enrolled at their first clinic visit. This analysis compares four groups of women categorized according to their own and their partners' employment status. Group 1 comprised women unemployed, partners not unemployed. Group 2 comprised women not unemployed with unemployed partners. Group 3 comprised women and partners who were both unemployed. In group 4 neither partner was unemployed. Initial analysis showed that there was a significant association between birthweight and birthweight for gestational age, and unemployment as reported by mothers. After adjustment for lifestyle variables (principally smoking) there were no remaining statistically significant associations.

The association between unemployment (in men) and lifestyle, mental and physical health has been reviewed by Kerr (1983) and Schwefel (1986), but there have been few reports regarding unemployment amongst women and more specifically the effect of unemployment on pregnant women and possible consequences for reproductive outcome. Such research is needed, in part, because of the recent increase in female unemployment. Between 1970 and 1986 there was a 15% increase in numbers of males employed and a 55% increase in numbers of females employed in Australia (Fisher 1987). The female unemployment rate in Australia has been higher than the male unemployment rate in 15 of the last 17 years, and according to Fisher (1987) in 1986 unemployed females comprised 42% of the total unemployed and 39% of the employed workforce.

The purpose of this study was to determine whether (i) unemployment of the pregnant woman affected pregnancy outcomes, (ii) unemployment of the pregnant woman's partner affected pregnancy outcomes, (iii) unemployment of both partners affected pregnancy outcomes, (iv) whether related factors, e.g. age, parity, smoking, etc. were intervening or confounding variables in any apparent association of the above events.

Subjects and methods

This paper reports data from the Mater–University of Queensland Study of Pregnancy (MUSP). It follows up a cohort of pregnant women enrolled and interviewed at their first clinic visit and for whom data on pregnancy outcomes were available from the hospital records.

Details of sampling, questionnaire design, response rates, etc. have been reported by Keeping *et al.* (1989). For this analysis demo-

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graphic and lifestyle data were taken from the questionnaire administered at the first clinic visit and details of the birth were abstracted from the medical record completed by hospital staff. Staff completing this record were effectively 'blind' to the unemployment status of the respondent.

Employment status was determined on the basis of two precoded questions answered by the respondent. Unemployment status was determined by a respondent's subjective judgement that she or her partner or both were so categorized. While there is some debate about whether persons not in receipt of unemployment benefits are, in a strict sense, unemployed, it is clear that many persons seeking work are, for a variety of reasons, unable to obtain government benefits. It has been estimated that these 'hidden' unemployed are disproportionately women whose partners are employed and who, while wishing to work, have not been able to receive unemployment benefits.

Results

Of the 8556 women initially enrolled in the study 252 failed to provide employment details either for themselves or their partner and a further 136 women were excluded because they were pensioners (117), students (4) or other women (15) without a partner. Those women describing themselves as unemployed and without a partner (150) were categorized as unemployed, while those women employed but without a partner (77) were categorized as 'neither unemployed'. In any event, separate computer runs including and excluding the latter two groups did not influence the findings.

Table 1 provides details of the major subgroups in the comparisons which follow. Women who were themselves unemployed were distinguished from those who described their partners as unemployed and from those who were unemployed at the same time as their partners. While only 2·7% of the sample reported that both partners were unemployed, it seemed appropriate to treat separately this group of women who might be expected to manifest the most severe pathology, if such exists.

Table 1. Unemployment status*

	n	%
Mother unemployed	713	8·7
Partner unemployed	666	8·2
Both unemployed	224	2·7
Neither unemployed	6565	80·4
Total	8168	100·0

* Excluded were 158 for whom data on their unemployment status and that of their partners were missing.

Unemployment levels are not randomly distributed throughout the community but concentrated amongst some groups (Table 2). In our sample of 8168 women, some 65% of the 89 women who were aged ≤18 years were in one of the three unemployed groups, as were 24% of those women in the 19–25 age group ($n = 4678$). Similarly, the unemployed groups had lower parity, were less often married, were more often from the lowest occupational status group, had higher smoking levels and less regularly ate breakfast. In a number of respects the unemployed groups, particularly that group of women who reported themselves unemployed, had biological characteristics and health behaviours which suggested they were likely to have a less favourable outcome of their pregnancies.

Tables 3 to 5 present the mean and categorized comparisons of the pregnancy outcomes (gestation at delivery, birthweight, birthweight for gestation, and perinatal death) of the four groups, both unadjusted and adjusted for the potentially adverse biological and behavioural variables noted previously. It is clear that the unemployed groups do not experience higher levels or rates of preterm delivery (Table 3).

By contrast, the mean unadjusted birthweight of the unemployed groups is some 50–100 g lighter than that of the group with neither partner unemployed (Table 4). Adjustment using analysis of variance shows that this difference is largely attributable to the higher levels of smoking in the unemployed groups. While the pattern of rate of low birthweight follows broadly the comparisons of the means, these latter differences are not statistically significant.

The unemployed groups have babies with lower weight-for-gestation, and higher rates of babies under the 5th birthweight centile (Table 5). Adjustment for the mother's smoking levels is the single major factor contributing to a reduction of these differences, although adjustment for parity and eating breakfast regularly also contributes to the reduction of these differences, until they become of marginal statistical significance (reduced from $P<0{\cdot}0001$ to $P = 0{\cdot}11$). The major remaining difference,

Table 2. Association between unemployment status and socio-demographic and health behaviour variables

	Cramer's *V*
Mother's age	0·14***
Parity	0·15***
Marital status	0·30***
Partner's occupational status	0·10***
Smoking at first visit	0·09***
Eat breakfast regularly	0·07***

*** $P<0·001$.

after adjustment, appears to be between those women who report their partners are unemployed and the group where neither is unemployed.

In total there were 80 perinatal deaths in the sample, of which 16 occurred in the unemployed groups (rate 11·4 per 1000 births) compared with 64 deaths in the 'neither unemployed' group (rate 10·6 per 1000 births). These differences are modest and are attributable to chance. A sample of considerably greater size than the one obtained for this study would be required to confirm or deny the existence of the significance of difference observed above (Table 6).

Discussion

Work (next to sleep) is the second most important focus of day-to-day activity, although it is believed that the financial aspects are of relatively minor importance in influencing work satisfaction, compared with the feelings of accomplishment and self-respect (Converse 1980) and the development of a social network (Borrero & Rivera 1980). Conversely, lack of work has been associated with emotional and mental health problems as reported by Hill (1978), Zawadski & Lazarsfeld (1935), Linn *et al.* (1985) and Banks & Jackson (1982). Any association between lack of work and physical health is less clear.

Criticisms of the methods used in previous studies of the association between unemployment and health have been expressed by Ackerman & Vaeth (1978), Moser *et al.* (1984), Waldron *et al.* (1982) and McMichael (1976). For these reasons this review has been limited to papers with a longitudinal design and with reliably measured health outcomes.

Brenner (1977) and College (1982) used aggregate data to infer that a 1% increase in unemployment leads to a 2% increase in mortality, although Spruit (1982) raised doubts about these findings. Support for the association between unemployment and mortality has been provided by Moser *et al.* (1984) in the extensive OPCS longitudinal study covering 1% of the British population and specifically looking at various causes of death and allowing for social class differences. However, the association between unemployment and morbidity was less clear as the DHSS Cohort Study in Britain showed only an increased utilization of health services by the unemployed group (Ramsden & Smee 1981). Almost parallel findings were reported by the American Veterans' Administration Study, where despite greater use of medical services by the unemployed group, and a subjective decrease in their health, there was no significant increase in diagnosed illness. Cook *et al.* (1982) reported higher rates of lung and heart disease when unemployed were compared

Table 3. Unemployment status by preterm delivery

	Mean gestation (weeks)		Rate of preterm births (≤36 weeks)		
				Odds ratio	
	Unadjusted	Adjusted*	Rate/100 births	Unadjusted	Adjusted*
Mother unemployed	39·3	39·2	6·70	1·44	1·17
Partner unemployed	39·4	39·3	3·87	0·81	0·58
Both unemployed	39·3	39·1	5·73	1·22	0·76
Neither unemployed	39·3	39·2	4·75	1·00	1·00
	NS	NS		$P=0·10$	$P=0·12$

* Adjusted for mother's age, parity, marital status, father's occupational status and mother's smoking and eating breakfast regularly.

Table 4. Unemployment status by birthweight

			Rate of low birthweight (≤2499g)		
	Mean birthweight (g)		Rate/100 births	Odds ratio	
	Unadjusted	Adjusted*		Unadjusted	Adjusted*
Mother unemployed	3277	3327	6·54	1·31	1·27
Partner unemployed	3324	3296	5·63	1·11	1·03
Both unemployed	3287	3313	5·73	1·13	0·84
Neither unemployed	3380	3331	5·08	1·00	1·00
	$P<0·0001$	NS		NS	NS

* Adjusted for mother's age, parity, marital status, father's occupational status and mother's smoking and eating breakfast regularly.

with employed men, although adjustment for some socio-demographic and lifestyle variables reduced or eliminated the differences.

Few studies of unemployment and pregnancy outcome have been reported. In Australia, Lumley *et al.* (1985) noted that women with unemployed partners were more likely to have low birthweight babies. This has also been reported by Stein *et al.* (1987) in Oxford—a difference which was attributed to income.

In the longitudinal study we are presenting, a large sample of women were questioned early in pregnancy about their own and their partner's employment status. Four commonly accepted indicators of the outcome of pregnancy were obtained from the subsequent hospital record. Employment data were obtained early in pregnancy and it may be that some women (or their partners), initially categorized as employed or unemployed, subsequently changed their status. It appears unlikely, however, that the above process produced misleading results. Thus it is notable that the group possibly least subject to these changes of status (the 'father unemployed' group) manifests differences of magnitude similar to the other two unemployed groups.

The results suggest that for two of the four outcomes (birthweight and weight for gestational age) one or more of the unemployed groups had more adverse pregnancy outcomes. Adjustment for various biological and lifestyle factors indicated that the above differences were attributable to the higher rate of cigarette consumption and lower parity evident in the unemployed groups.

A number of subsidiary findings also warrant comment. Women who are themselves unemployed (as well as women whose partner is unemployed) appear to be at greater risk of having a low-birthweight and small-for-gestational-age baby. The unemployment status of both partners is pertinent to understanding the outcome of a pregnancy.

This study suggests that the observed differ-

Table 5. Unemployment status by birthweight centile adjusted for gestational age

			Rate of low birthweight (≤5th centile)		
	Mean birthweight centile		Rate/100 births	Odds ratio	
	Unadjusted	Adjusted*		Unadjusted	Adjusted*
Mother unemployed	44·5	47·6	6·39	1·48	1·16
Partner unemployed	47·0	45·8	6·69	1·56	1·50
Both unemployed	45·0	47·9	5·73	1·32	0·86
Neither unemployed	50·6	49·0	4·40	1·00	1·00
	$P<0·0001$	$P = 0·11$		$P = 0·02$	NS

* Adjusted for mother's age, parity, marital status, father's occupational status and mother's smoking and eating breakfast regularly.

Table 6. Unemployment status by perinatal death

	Perinatal mortality			
			Odds ratio	
	Rate/1000 births	(*n*)†	Unadjusted	Adjusted*
Mother unemployed	15·6	(10)	1·47	1·41
Partner unemployed	8·8	(5)	0·83	0·67
Both unemployed	5·2	(1)	0·49	0·49
Neither unemployed	10·6	(64)	1·00	1·00
			NS	NS

* Adjusted for mother's age, parity, marital status, father's occupational status and mother's smoking and eating breakfast regularly.

† Number of deaths.

ences in pregnancy outcome are attributable to known risk factors which are more common in the unemployed groups. While it is not possible to assert confidently a particular cause–effect sequence from this study alone, it is possible to combine the findings of this study with others of the unemployed to describe the most likely causal sequence (see Zawadzki & Lazarsfeld 1935; Kasl *et al.* 1975; Hill 1978; Borrero 1980; Banks & Jackson 1982; Burke 1984; Linn *et al.* 1985; Kessler *et al.* 1987). While the process will vary somewhat for particular individuals and groups, it appears the unemployed react initially to their changed status by enthusiastically seeking work. As such efforts meet with repeated rejection, their economic circumstances decline, and their emotional state deteriorates. Many of the unemployed become apathetic and depressed, some react by choosing to use substances which may temporarily elevate their mood (e.g. cigarettes). If this projection above is correct, then unemployment can be seen to induce a variety of changes in lifestyle, some of which may have a negative influence on the outcome of pregnancy.

That these differences are attributable to known risk factors (e.g. cigarette smoking, parity) does not diminish the value of perceiving the unemployed group to be at elevated risk. There may be a need to mount pre-emptive surveillance and appropriate health education programmes, as well as dealing creatively with the social rejection implied by unemployment status.

We conclude that there is an association between unemployment and low birthweight. These differences appeared largely attributable to the observation that women in the unemployed groups had higher rates of cigarette consumption. Because unemployment appears to have an adverse influence on a mother's lifestyle there is a need to consider the benefits of prevention programmes for these women.

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C-reactive protein in preterm labour: association with outcome of tocolysis and placental histology

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Summary. Tocolytics were administered in 66 consecutive women in uncomplicated preterm labour with intact fetal membranes (53 singleton and 13 twin pregnancies). C-reactive protein (CRP), a marker of infection, was determined daily and used retrospectively to investigate the role of subclinical infection in preterm labour and to predict the efficacy of tocolysis and the development of a clinical perinatal infection. CRP was also determined in 66 women in uncomplicated labour at term (53 singleton and 13 twin pregnancies). The placenta was examined for histological evidence of infection in all patients who were delivered before 36 weeks (n=21) and in all women in the control group (n=66). Elevated CRP levels were more often found in patients who were refractory to tocolysis, suggesting an underlying infectious morbidity. Placental infection was found in 62% of the preterm delivery group and in 12% of the control group. There was an association between elevated CRP levels and histological evidence of placental infection. However, confounding factors such as urinary tract infections limit the usefulness of the CRP test. Because CRP cannot predict clinical perinatal infection accurately, its clinical relevance is very limited.

Increasing emphasis is being placed on the role of subclinical amnionitis in the aetiology of 'idiopathic' preterm labour. It is now generally accepted that during preterm labour, intact membranes are not an insurmountable barrier against ascending invasion of genital tract bacteria (Minkoff 1983). Subclinical infection was frequently shown to interfere with the efficacy of tocolysis (Bobitt *et al.* 1981). Handwerker *et al.* (1984), Hameed *et al.* (1984) and Potkul *et al.* (1985) have used a rise in the plasma level of C-reactive protein (CRP) in woman in preterm labour with intact fetal membranes as an early marker of infection. They found an association between raised serum CRP, failed tocolysis and histological signs of amnionitis.

Tillett & Francis (1930) noted that during an acute febrile illness the patient's serum precipitated with an extract of pneumococcus (C-protein). The substance responsible for pre-

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cipitation was a plasma globulin of hepatic origin (C-reactive protein). This 'acute phase reactant' is non-specific, and a raised CRP level can be diagnostic of any active infection or tissue necrosis (Gewurz *et al.* 1982).

We wished to assess the usefulness of serial CRP determinations in idiopathic preterm labour in diagnosing subclinical amnionitis and predicting the efficacy of tocolysis and the occurrence of clinical perinatal infection. Because twin pregnancies are more liable to preterm labour and amniotic fluid infection (Naeye & Ross 1982), a number of twin pregnancies were included in the study

Patients and methods

The study group comprised 53 consecutive singleton pregnancies and 13 consecutive twin pregnancies in white European women who fulfilled the criteria for enrolment in the study. All of them were patients admitted in preterm labour to the maternity ward of the Academic Hospital between 1 April 1984 and 30 September 1986 and they were all considered suitable for tocolysis. Criteria for inclusion in the study were: intact fetal membranes, gestational age between 22 and 35 weeks (based on reliable menstrual dates or first trimester ultrasonography or both), regular painful uterine contractions at least one in 5 min, cervical dilatation <3 cm, no detectable fetal distress, no contraindications to intravenous ritodrine, no clinical signs of amnionitis, no use of antibiotics or tocolytics before admission.

Serum levels of CRP were measured daily by laser nephelometry, making use of a LAS-R Nephelometer PDQ Instrument, LAS-R Multiparameter Reference Serum (human origin) and specific C-reactive protein Laser-R antiserum (Baxter Travenol Laboratories, Inc.). A positive CRP was defined as a serum level >1·25 mg/dl. The CRP levels were not available to the obstetricians on duty so as not to influence the management of the patient.

A clean-caught urine specimen was taken on admission for analysis and culture. Asymptomatic bacteriuria was defined as the presence of $\geq 10^5$ bacteria/ml without symptoms. Cystitis was defined as $\geq 10^5$ bacteria/ml in the presence of urgency, frequency and/or dysuria but in the absence of flank pain, fever and chills.

Management included bed-rest and tocolysis with intravenous ritodrine (50 to 300 µg/min) followed by oral ritodrine. Tocolysis was interrupted if cervical dilatation progressed to ≥4 cm, if the membranes ruptured or if fetal distress or serious maternal discomfort occurred. We considered tocolysis to have 'failed' when delivery took place within 1 week after the start of treatment and to have succeeded when delivery was postponed by ≥1 week. If (initially successful) tocolysis had to be reinstated after more than 1 week, it was considered as a new attempt to stop labour.

Our control group consisted of 53 consecutive uncomplicated singleton pregnancies and 13 consecutive uncomplicated twin pregnancies in white European women admitted, at term, in the active phase of labour (cervical dilatation >4 cm) with intact fetal membranes followed by a spontaneous first stage. The plasma level of CRP was determined on admission.

The placenta was examined in all of the 21 women who were delivered before 36 weeks and in all 66 women in the control group Placentas were assessed by A. G. (who was not aware of the study) according to the criteria described by Blanc (1981) and categorized as: stage I (intervillositis): maternal neutrophils attached to the underside of the placental plate; stage II (chorionitis): migration of neutrophils into the plate; stage III (chorioamnionitis): neutrophils reaching the amnion. In twin pregnancies the placenta of the first-born twin was used for histological staging.

The Mann–Whitney *U*-test was used for comparing the continuous variables in the preterm and the control group The χ^2-test with Yates' correction or Fisher's exact test were used for evaluating the association of CRP with placental histology, urinary tract infection and preterm or term delivery. The level of statistical significance was set at $P=0{\cdot}05$. Sensitivity, specificity, predictive value of a positive and negative test were determined as described by Stempel (1982) to indicate the value of CRP as a predictor for preterm birth and perinatal infection.

Results

There were 60 attempts at tocolysis in the 53 singleton pregnancies and 49 were successful. In the twin group 19 attempts were made, of which 13 were successful. The mean gestational age at the start of tocolysis was higher in the pregnancies where treatment succeeded than in those

Table 1. Relation of gestational age (weeks) to outcome of tocolysis

		Gestational age (weeks)	
Outcome of tocolysis	No. of attempts	At admission Mean (SD)	At delivery Mean (SD)
Singleton pregnancies	60		
Successful	49	31·0 (2·8)	38·4 (1·8)
Failed	11	28·7 (4·3)	28·9 (4·4)
Significance of difference*		NS	*P*<0·001
Twin pregnancies	19		
Successful	13	29·5 (3·9)	34·2 (4·4)
Failed	6	28·5 (4·2)	28·8 (4·2)
Significance of difference*		NS	*P*<0·025

* Mann–Whitney test (α=5%).

where it failed but the difference was not statistically significant (Table 1).

The predictive value of CRP for the outcome of tocolysis is shown in Table 2. In singleton pregnancies the predictive value of a positive CRP on admission was 64% which means that there were 36% false-positive values. In twin pregnancies the predictive value of a positive test was only 17%. Daily determination of CRP did not greatly improve the predictive value of a

Table 2. Accuracy of serum C-reactive protein (CRP) estimations in singleton and twin pregnancies as a predictor of outcome of tocolysis in preterm labour*

	Tocolysis in singleton pregnancies			Tocolysis in twin pregnancies		
Test result	Failed (*n*=11)	Succeeded (*n*=42)	Total (*n*=53)	Failed (*n*=6)	Succeeded (*n*=7)	Total (*n*=13)
Positive CRP						
A	7	4	11	1	5	6
B	9	7	16	5	4	9
C	9	1	10	5	2	7
Negative CRP						
A	4	33	42	2	5	7
B	2	35	37	1	3	4
C	2	41	43	1	5	6

	CRP test in singleton pregnancies			CRP test in twin pregnancies		
	A	B	C	A	B	C
Sensitivity (%)	64 (45–74)	82 (65–90)	82 (66–90)	33 (7–65)	83 (50–99)	83 (50–99)
Specificity (%)	90 (88–97)	83 (65–90)	98 (85–100)	50 (19–81)	43 (15–78)	71 (35–93)
Predictive value of positive CRP (%)	64 (30–91)	56 (27–73)	90 (55–100)	17 (1–50)	56 (22–85)	71 (35–93)
Predictive value of negative CRP (%)	90 (76–97)	95 (83–99)	95 (83–99)	71 (35–93)	75 (30–91)	83 (50–99)

The values in parenthesis show the approximate 95% confidence intervals.

A, Positive CRP on admission; B, positive CRP on admission or during hospitalization; C, positive CRP as for B, but after elimination of confounding factors.

* Failed tocolysis defined as delivery within 1 week of start of treatment, and successful tocolysis defined as delivery postponed by ≥1 week

Table 3. Association between time of delivery and placental histology

Placental histology	Preterm delivery (n=21)	Term delivery (control group) (n=66)
Negative	8 (38%)	58 (88%)
Positive	13 (62%)	8 (12%)
Stage I	4/13 (31%)	6/8 (75%)
Stage II	2/13 (15%)	2/8 (25%)
Stage III	7/13 (54%)	0/8 (0%)

Significance of difference between the two groups: $P<0{\cdot}001$ (χ^2-test)

positive test in singleton pregnancies, but it markedly improved the predictive value in twin pregnancies.

'Confounding factors' were identified where a positive CRP was associated with an infection other than 'amnionitis'. The most important of these confounding factors was a urinary tract infection In the study group, 11 of the 66 women (17%) had a urinary tract infection, and seven of them had positive CRP levels (P=0·0027, Fisher's exact test); of these seven women, four (two singleton and two twin pregnancies) had asymptomatic bacteriuria and three (two singleton and one twin pregnancy) had cystitis. All the infections were treated and all seven positive CRP reactions became negative. In the singleton group one woman developed an acute bronchitis and another a superficial thrombophlebitis while in hospital; both women had positive CRP values which became negative after appropriate therapy. No other confounding factors were noted. After elimination of those confounding factors, both the specificity and the predictive value of a positive CRP test improved (Table 2).

The relation between CRP, placental histology and preterm or term delivery is shown in Tables 3 and 4. In nine of the 13 preterm singleton deliveries the membranes were ruptured artificially; in the other four the membranes ruptured spontaneously preterm. Of the eight preterm twin deliveries the membranes ruptured spontaneously in four and were ruptured artifically in the other four The mean interval between membrane rupture and delivery was 5·3 h and only two women had an interval of >12 h. In the control group the mean interval between artificial membrane rupture and delivery was 2·6 h. Histological evidence of placental infection ('positive' histology) was present significantly more often in the preterm group than in the control group (Table 3). Moreover, in the preterm delivery group, stage III (chorioamnionitis) predominated, whereas in the control group, stage I (intervillositis) was found most often. The distribution of positive CRP values showed a similar trend: they occurred more often in the preterm group than in the control group (Table 4). Most CRP values in the preterm group were >2·5 mg/dl (twice the cut-off value of 1·25 mg/dl), whereas there was only one CRP value >2·5 mg/dl in the control group.

At first sight there appears to be an association between positive CRP values and positive placental histology both in the preterm and term delivery groups. In fact, 12 of the 13 women (92%) who were delivered preterm with histological signs of placental infection had a positive CRP (P=0·003, Fisher's exact test), whereas only two of the eight (25%) women delivered at term with a positive placental histology had positive CRP values (not significant).

Preterm delivery occurred more often in twin pregnancies than in singleton pregnancies, yet the frequency of amnionitis was similar in both groups (Table 5).

The 21 preterm deliveries resulted in 29 babies; 11 of these died an early neonatal death, mostly as a result of prematurity Only three neonatal deaths were directly attributable to fetal infection (congenital pneumonitis in two and sepsis with shock in one). One of the surviving infants had purulent conjunctivitis. No other infections were diagnosed within 3 days of birth.

In the preterm delivery group three women developed intrapartum pyrexia (>38°C): in each of them the membranes had ruptured and fever was noted within 2 h before delivery. These women were considered to have clinical amnionitis as no other identifiable source of infection was identified. Intrapartum pyrexia

Table 4. Association between the time of delivery and C-reactive protein (CRP) serum levels

Serum CRP (mg/dl)	Preterm delivery (n=21)	Term delivery (control group) (n=66)
<1·25	7 (33%)	47 (71%)
1·25–2·5	1 (5%)	18 (27%)
>2·5	13 (62%)	1 (2%)

Significance of difference between the two groups $P<0{\cdot}001$ (χ^2-test)

Table 5. Comparison of histological evidence of placental infection between singleton and twin pregnancies delivered preterm

	Preterm delivery (<36 weeks)	Positive placental histology	
		All stages	Stage III only
Singletons	13/53 (25%)	8/13 (62%)	4/13 (31%)
Twins*	8/13 (62%)	5/8 (63%)	3/8 (38%)
Significance (*P*)	<0·05	NS	NS
Test	χ^2	(Fisher's exact test)	

* Only the placenta of the first twin is taken into consideration.

(>38°C) was not seen in the control group. Postpartum endometritis occurred in two women in the preterm delivery group but in none in the control group. The value of CRP as a predictor of clinical perinatal infection is shown in Table 6.

Discussion

There is a greater risk of failure of tocolysis at earlier gestational ages (Table 1), but in contrast to other studies (Bobitt *et al.* 1981; Handwerker *et al.* 1984) in our series the difference was not statistically significant. It has been suggested (Naeye & Ross 1982) that the risk of amnionitis is greater at a lower gestational age because there is less antimicrobial activity in the amniotic fluid.

In preterm labour with intact fetal membranes, elevated CRP levels are associated with histological signs of infection; both are a reflection of a subclinical amnionitis. Our findings that CRP is an acceptable predictor of the outcome of tocolysis confirm previous reports (Hameed *et al.* 1984; Handwerker *et al.* 1984; Potkul *et al.* 1985). The predictive value of a positive and a negative test is useful because of its clinical relevance. Our CRP results in singleton pregnancies on admission are comparable to those found by Handwerker *et al.* (1984) (PPV: 73%; NPV: 94%) and by Potkul *et al.* (1985) (FPV: 62·5%; NPV: 95·8%). Our false-positive values in singleton pregnancies range from 10 to 40%, and in twin pregnancies from 29 to 83% depending on the criteria used (Table 2). This wide variation is due to the smaller number of twin pregnancies and must be regarded with some caution. However, our findings suggest that it is important to define the conditions of the CRP test before using the results and this certainly limits its clinical applicability. It is most important to eliminate confounding factors, in particular urinary tract infections. Handwerker *et al.* (1984) considered that urinary tract infection was not a confounding factor, although three out of four of their patients with false-positive test results (positive CRP and successful tocolysis) had a urinary tract infection Overall 40% of their patients had a urinary tract infection but their definition of a positive urine analysis was not specified. Potkul *et al.* (1985) excluded patients with urinary infections (8%) from their analysis. In our singleton pregnancies, serial determinations did not improve the clinical usefulness of the CRP test but the opposite was true in the twin pregnancies. This is because most of the singleton pregnancies with positive CRP reactions were already positive on admission but only one of the twin pregnancies presented with a positive CRP, the others became positive while in hospital. Serial determinations enabled us to follow the development of an underlying subclinical infection by the gradual rise of CRP followed by delivery in most women.

CRP levels increase during normal pregnancy and in particular during labour (Romem & Artal 1985). The reason for this is unclear. During labour, due to an increase in natural killer cell activity, interleukin-1 (a leucocyte endogeneous mediator) is produced which can induce the formation of CRP in hepatocytes (Keleman *et al.*

Table 6. Diagnosis of perinatal infection by means of maternal serum C-reactive protein (CRP) estimations

Perinatal infection	Positive CRP (>1·25 mg/dl)	Negative CRP (≤1·25 mg/dl)	Total
Present	4	3	7
Absent	11	48	59
Total	15	51	66

Sensitivity = 57% (22–85) Specificity=81% (68–89). Predictive value of a positive CRP=26% (7–55) Predictive value of a negative CRP=94% (85–99). (The figures in parenthesis are the approximate 95% confidence intervals.)

1986). Bejar *et al.* (1981) noted that a number of genital tract bacteria produce phospholipase A_2 which activates the prostaglandin cascade and may initiate preterm labour. Kelemen *et al.* (1986) suggested that prostaglandins could increase the liberation of CRP although it is more likely that the increased levels of CRP in preterm labour are primarily a consequence of infection. In the control group of patients in active labour, in the maintenance of which prostaglandins play an important role, only one patient had a CRP level above 2·5 mg/dl (Table 4) whereas most women delivered preterm had CRP levels >2·5 mg/dl. It is likely that subclinical infection accounted for a 'superimposed' CRP elevation in the failed tocolysis group.

A raised CRP was associated with a positive placental histology in the preterm delivery group, but not in the control group. This may be explained by the different mechanism of onset of labour; in the control group with positive histology it is possible that labour preceded infection and the CRP was not yet elevated (levels rise about 6 h after onset of infection (Gewurz *et al.* 1982)) and placental histology was mostly limited to intervillositis. In contrast, in the preterm delivery group with positive histology, it is possible that infection preceded labour so that when labour became established the infection was already present for some time. This is shown by a greater increase in CRP values and by a further migration of maternal neutrophils into the placental plate (Tables 3 and 4).

Neonatal complications in our series were mostly related to preterm birth and not to infection. Exposure to bacteria therefore does not necessarily mean that the baby will be infected. The same is true for maternal perinatal infectious morbidity; only some of the women with subclinical infection will actually develop clinical signs of infection. CRP testing is insufficient for identifying those patients at risk (Table 6).

In conclusion, a raised serum CRP is an acceptable predictor of the efficacy of tocolysis and a marker of subclinical amnionitis only after the elimination of confounding factors. However, a raised serum CRP is not a reliable predictor of clinical perinatal infectious morbidity and will not alter our management of women in preterm labour with intact membranes. The clinical usefulness of CRP is very limited.

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Placental hormones and maternal glucose metabolism. A study of fetal growth in normal pregnancy

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Summary. The interrelations between three placental hormones (oestradiol, progesterone and hPL), maternal glucose metabolism, maternal anthropometry and fetal growth were studied in a sample of 52 carefully selected pregnant women. A relation was found between infant birthweight and both fasting blood glucose and $t_{\frac{1}{2}}$ of glucose of an intravenous glucose tolerance test at week 37 of pregnancy. The serum concentrations of the placental hormones were not significantly related to the glucose variables. The correlation between birthweight and the maternal levels of hPL in late pregnancy ($r = 0{\cdot}60$) persisted when fasting blood glucose and $t_{\frac{1}{2}}$ of glucose were taken into account. Maternal fat mass was found to explain more of the variation in basal insulin levels around week 37 than did the placental hormones.

Recent studies on offspring of twins in a Scandinavian population have provided evidence that the major part of the variation in birthweight is genetic (Magnus *et al.* 1984). A possible explanation for the wide variation of birthweights in normal pregnancy could be the physiological variation in maternal glucose metabolism. Altered insulin levels and response to food ingestion during late pregnancy favour fetal growth by delaying the deposition of ingested nutrients and by increasing the generation of fuels from maternal stores when fasting (Freinkel 1980). Thus, a genetically determined variation in maternal metabolic efficiency during pregnancy, reflected in carbohydrate metabolism, could well be associated with the variation in birthweight.

The classic placental hormones, human placental lactogen (hPL), oestradiol and progesterone, have been found to be associated with the change in glucose metabolism which takes place during pregnancy (Kuhl *et al.* 1984). hPL and oestradiol are also correlated with placental function and fetal growth. The question thus arises: are placental hormones related to birthweight by their effect on maternal glucose metabolism?

Maternal fat mass has been found to correlate with insulin levels in late pregnancy (Karam *et al.* 1963). The placental hormones have also been suggested to increase the secretion of insulin (Hornnes 1985). Hence, it seemed to be of interest to study the relative contribution of maternal fat mass and placental hormones to the elevated insulin levels in late pregnancy. Knowledge of factors that affect glucose tolerance in late pregnancy might also be relevant for the understanding of the development of gestational diabetes.

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Table 1. Characteristics of the 52 women in the study who gave birth at term after an uncomplicated pregnancy

Characteristics	Mean (SD)	Range
At onset of pregnancy:		
Age (years)	28·7 (4·7)	21–40
Prepregnancy weight (kg)	61·6 (9·9)	39·0– 95·0
Height (cm)	167·1 (6·0)	155–180
At week 37:		
Body-weight (kg)	75·5 (10·6)	57·8–103·5
Fat mass (kg)	23·8 (6·5)	13·5– 42·2
At delivery:		
Gestational age* (days)	282 (8)	259–294
Birthweight (g)		
Unadjusted	3721 (586)	2620–6020
Adjusted†	3668 (498)	2850–5810
Placental weight (g)	643 (155)	380–1090

* Calculated from ultrasound measurement in week 17.

† Adjusted for gestational age.

Subjects and methods

This paper is part of a comprehensive investigation of energy metabolism during pregnancy in Swedish women. Details of the overall study design have been published by Langhoff-Roos *et al.* (1987). In brief, 56 healthy Swedish women selected to obtain a wide variation in expected birthweight and undergoing a normal second pregnancy leading to a term birth formed the basis for this study. Four of them did not complete the planned investigations, leaving only 52 for assessment.

Anthropometry

Maternal fat mass in early pregnancy was calculated using prepregnancy weight and four skinfold thicknesses (biceps, triceps, subscapular and suprailiac) at week 17, according to the equations given by Durnin & Womersley (1974). Similarly, fat mass at week 37 was calculated using body-weight and skinfold measurements in week 37. (Measurements of skinfold thicknesses were missing in one woman at week 37.) Lean body mass was calculated as the difference between body-weight and fat mass. Infant birthweight was obtained immediately after birth and adjusted for gestational age by adding or subtracting 30 g multiplied by the number of days the date of delivery deviated from the date predicted by ultrasound measurement at week 17 (Persson & Weldner 1986).

Blood samples

Samples of maternal blood were collected from the antecubital vein into a glass test-tube in the non-fasting state in the afternoon in week 37. The test-tubes were left at room temperature for about 1 h and stored at 7°C for $\leq$24 h before centrifugation for 10 min at 6000 r/min. Serum was separated and stored for $<$1·5 years at −70°C before analysis.

Intravenous glucose tolerance test

At week 37, an intravenous glucose load of 0·35 g/kg maternal body-weight was given at 08.00 hours. The procedure was performed on an outpatient basis. Before the glucose load a fasting blood glucose value was determined. Glucose was infused as a 25% (w/v) solution during 2·5 min, and capillary blood glucose was measured every 10 min for the first hour thereafter. Blood glucose was analysed enzymatically and the half-time of glucose elimination ($t_{\frac{1}{2}}$ of glucose) was estimated.

Levels of insulin were analysed in serum taken at −5, 0, 4, 6, and 60 min from the start of the procedure. Serum insulin was determined by a radioimmunoassay technique. Fasting insulin was calculated as the mean of the two basal levels, and peak insulin as the mean of the 4- and 6-min values. The insulin rise was defined as the ratio between absolute values of peak insulin and fasting insulin. The level of insulin at the end of the test was called the 1-h insulin.

Assessment of serum levels of oestradiol, progesterone and hPL

Oestradiol and progesterone concentrations were determined by radioimmunoassay at the department of obstetrics and gynaecology, University Hospital, Uppsala, Sweden (Lindberg *et al.* 1974; Thorneycroft & Stone 1972). hPL was measured by radioimmunoassay at Pharmacia Diagnostics, Uppsala (Lindberg & Nilsson 1973).

Statistics

Statistical analyses, including multiple linear regression, used the SAS program (1985). In the

Table 2. Glucose and insulin results obtained in the intravenous glucose tolerance test at 37 weeks

Index	Mean (−2SD, +2SD)	Range
Glucose		
Fasting (mmol/l)	4·62 (3·78, 5·46)	3·6–5·4
$t_{\frac{1}{2}}$ (min)	41·3 (35·3, 57·3)	26–65
Insulin*		
Fasting (mU/l)	12·7 (5·3, 26·3)	4·3–34·0
Peak (mU/l)	110·4 (38·9, 257·0)	30·5–285·0
After 1 h (mU/l)	26·0 (8·1, 64·6)	7·6–89·0
Rise (—)	9·2 (1·6, 16·8)	2·4–21·3

* Insulin levels are antilogged values from the distribution of logarithmized values.

Tables the standard errors of the mean have been omitted, since they can be calculated from the given n, mean and P-value. Values of placental hormones and insulin concentrations were converted to logarithms.

Results

The main characteristics of the women who took part in the investigation are shown in Table 1. There was a wider variation in infant birthweight in the study sample than in the general Swedish population.

Birthweight and glucose values

The mean glucose and insulin values obtained in the intravenous glucose tolerance test are shown in Table 2. Birthweight was positively correlated with fasting blood glucose, and negatively correlated with the insulin rise (Table 3).

Figure 1 shows the mean (SD) values of fasting blood glucose and $t_{\frac{1}{2}}$ of glucose in three birthweight groups corresponding to the 10th and 90th centiles for multiparae in our population (unpublished data). It can be seen that the linear correlations between birthweight and the glucose variables are not solely caused by higher values in women who gave birth to large babies.

Birthweight and placental hormones

Table 4 gives the mean and the mean ± 2 SD values of the distributions of the logarithms of the serum concentrations of the placental hormones.

The interrelations between the three hormones (oestradiol, progesterone and hPL) were estimated by linear correlations. hPL correlated positively with both progesterone ($r = 0·38$) and oestradiol ($r = 0·22$), although only the correlation between hPL and progesterone was statistically significant ($P = 0·006$). Oestradiol and progesterone were not correlated ($r = 0·03$).

The relations between the three placental hormones and birthweight are shown in Table 5. Both correlation analysis and multiple linear regression showed that hPL was strongly positively related to birthweight ($P<0·001$).

Placental hormones and glucose values

In Table 6, birthweight has been analysed by multiple linear regression, using oestradiol, progesterone, hPL, and $t_{\frac{1}{2}}$ of glucose/fasting glucose as independent variables. Only hPL and one of the glucose values were significantly related to birthweight. (When both glucose values were used at the same time as independent variables, one of them lost the significant correlation to

Table 3. Correlation between birthweight and indices of glucose metabolism

	Glucose		Insulin		
Birthweight	Fasting	Elimination ($t_{\frac{1}{2}}$)	Fasting	Rise	1-h
r	0·42	0·36	0·24	−0·43	0·21
P	0·01	0·01	0·09	0·01	0·13

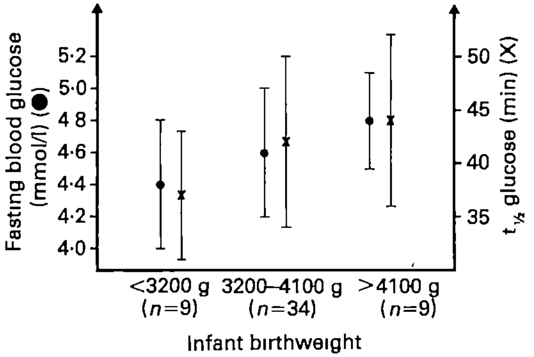

Fig. 1. Birthweight and two indices of glucose metabolism in 52 women. The mean ± SD values are shown for three different birthweight groups which correspond to birthweights below the 10th centile, between the 10th and 90th centile and above the 90th centile for multiparae in the Swedish population.

birthweight due to the significant correlation between the glucose values.)

Glucose tolerance

Placental hormones. Each of the indices of glucose metabolism was analysed by multiple linear regression using maternal levels of oestradiol, progesterone and hPL as independent variables (Table 7a). hPL was found to be positively (not significantly) related to fasting glucose, $t_{1/2}$ of glucose and 1-h insulin ($P = 0{\cdot}05$, $P = 0{\cdot}11$ and $P = 0{\cdot}09$, respectively). Progesterone was negatively (not significantly) related to fasting glucose ($P = 0{\cdot}10$).

Placental hormones and maternal fat mass

In Table 7b, maternal fat mass was added to the independent variables in the multiple linear regression analyses presented in Table 7a. By this procedure only minor changes in the relations between the placental hormones and indices of glucose metabolism took place (not shown). The coefficients of determination of fasting insulin and 1-h insulin were more than doubled, when maternal fat mass was added as an independent variable.

Discussion

All pregnancies in this study were normal and at term. Thus relations found between placental hormones, indices of glucose metabolism and birthweight can be considered to be valid within the physiological range. What is discussed is not whether a certain hormone or pathological glucose level has any effect on a specific target, but rather whether their variation within the physiological range is reflected in the variation of the other variables studied.

Birthweight

In these apparently healthy women, birthweight was found to be related to values of fasting blood glucose, $t_{1/2}$ of glucose and insulin rise in the intravenous glucose tolerance test measured at 36 weeks gestation. Although the extremes of this pattern could be considered characteristic of gestational diabetes, the existence of such a relation among healthy pregnant women has been a matter of controversy (Tallarigo *et al.* 1986; Letters 1987). In large infants, e.g. in gestational diabetes, placental glucose transfer is thought to stimulate fetal insulin secretion and fetal growth (Pedersen 1977). In women giving birth to small infants low glucose levels may reflect an insufficient supply of nutrients to the fetus (Abell 1979).

Considering the placental hormones, it was found that only hPL was independently correlated with birthweight. The question is whether hPL is a factor for fetal growth in late pregnancy, either directly or through an influence on maternal glucose metabolism. Another possibility is that hPL is only an indirect measure of active placental tissue and plays no direct role in fetal growth, in spite of its similarity with prolactin and growth hormone, and in spite of the high concentrations of hPL in the maternal circulation compared with that of other hormones in pregnancy.

The placental hormones have been suggested to affect maternal glucose metabolism in late pregnancy, both by increased secretion of insulin and increased insulin resistance (Kühl *et al.* 1984). Consequently the question arose

Table 4. Serum concentrations of oestradiol, progesterone and hPL in 52 healthy women in their second pregnancy at 37 weeks

Hormone	Mean	Mean ± 2 SD
Oestradiol (nmol/l)	53·8	27·4±106
Progesterone (nmol/l)	214	121±378
hPL (mg/l)	7·18	4·4±11·8

Results are antilogged values for the distribution of logarithmized values.

Table 5. Relation between birthweight (g) and maternal serum levels of oestradiol (nmol/l), progesterone (nmol/l) and hPL (mg/l) in week 37

	Birthweight			
	Correlation coefficient	*P*-value	Regression coefficient	*P*-value
Oestradiol	0·22	0·12	22	0·58
Progesterone	0·05	0·75	−824	0·10
hPL	0·60	0·001	3077	0·001
Coefficient of determination			40·6%	

Correlation coefficients and corresponding *P*-values are shown in the first two columns, followed by regression coefficients of the levels of hormones on adjusted birthweight by multiple linear regression and the corresponding *P*-values.

whether hPL might be associated with birthweight through its action on maternal glucose metabolism. By multiple linear regression it was found that even when the effect of the glucose values was considered, hPL was still highly significantly related to birthweight. Although the characteristics of a single glucose tolerance test at week 37 do not provide complete information on maternal glucose metabolism, it is evident that hPL is essentially related to infant birthweight by another mechanism.

hPL is produced in the syncytiotrophoblast and can be demonstrated in maternal blood in early pregnancy, and from mid-pregnancy onward it is also found in the fetal circulation at about 1% of the maternal levels (Osanthanondh & Tulchinsky 1980). hPL in the fetus has properties similar to those of human growth hormone in postnatal life. It stimulates the production of insulin-like growth factor (IGF 1) (Millner & Hill 1984). Thus, provided that there is a significant correlation between maternal and fetal levels of hPL, maternal hPL could reflect the circulating level of growth-stimulating activity in the fetus. A statistically significant correlation between maternal and fetal serum levels of hPL was not confirmed by Crosignani *et al.* (1972), whereas a close correlation was found between levels in maternal serum and amniotic fluid.

The level of hPL in maternal blood at week 37 is correlated with the size of the placenta at term. Furthermore, the placenta can be perceived as a fetal organ, and the size of the placenta close to term is inevitably strongly correlated with birthweight. Thus the correlation between maternal levels of hPL and birthweight is not necessarily cause and effect. Instead, hPL might be seen as a marker for functioning placental tissue and thereby the size of the fetus.

Insulin resistance

Insulin resistance is increased during the last part of pregnancy (Freinkel 1980). Higher insulin resistance implies that a greater amount of insulin is needed in order to keep serum con-

Table 6. Multiple linear regression analysis of birthweight (g) with serum levels in week 37 of oestradiol (nmol/l), progesterone (nmol/l), hPL (mg/l) and $t_{\frac{1}{2}}$ of glucose (min) and fasting glucose (mmol/l) as independent variables

	Birthweight			
	Regression coefficient	*P*-value	Regression coefficient	*P*-value
Oestradiol	31	0·42	410	0·27
Progesterone	−748	0·12	−527	0·26
hPL	2790	0·001***	2554	0·001***
$t_{\frac{1}{2}}$ of glucose	15·0	0·03*	8·7	0·24
Fasting glucose			299	0·04*
Coefficient of determination	46·1%		50·8%	

Table 7. (a) Regression coefficients, corresponding *P*-values and coefficients of determination from multiple linear regression analyses of maternal levels of oestradiol, progesterone and hPL on indices of glucose metabolism. (b) Coefficients of determination from multiple linear regression analyses of maternal levels of the above-mentioned placental hormones, plus maternal fat mass, on indices of glucose metabolism

	Fasting glucose (mmol/l)	$t_{\frac{1}{2}}$ of glucose (min)	Fasting insulin (mU/l)	Rise of insulin (—)	Peak insulin (mU/l)	1-h insulin (mU/l)
(a)						
Oestradiol	−0·48	−6·0	0·08	1·10	0·16	0·17
(nmol/l)	0·25	0·45	0·65	0·77	0·44	0·42
Progesterone	−0·85	−5·1	0·21	0·12	0·19	0·17
(nmol/l)	0·10	0·61	0·33	0·98	0·46	0·42
hPL	1·19	19·0	0·31	−7·9	−0·21	0·54
(mg/l)	0·05	0·11	0·22	0·15	0·50	0·09
Coefficient of determination	10·1%	5·6%	9·0%	4·9%	2·2%	12·1%
(b)						
Coefficients of determination	17·2%	5·7%	30·1%	10·8%	3·4%	32·9%

centrations of glucose at a constant level. Only a crude estimate of the resistance can be obtained by means of an intravenous glucose tolerance test. Those characteristics which primarily reflect the insulin resistance are fasting insulin and insulin 1 h after glucose administration. Eventually, however, all of the aspects of the test are affected by the insulin resistance.

The effects of hPL, oestradiol and progesterone on insulin secretion and resistance have been investigated in studies on man and animals. All three hormones have in one or several of these studies been correlated to increased insulin resistance (Hornnes 1985). In all earlier studies the hormones have been given to the subjects or added to cell cultures. The present study is the first to investigate whether the physiological variations of hPL, oestradiol and progesterone in late pregnancy are related to insulin levels. The results (Table 7) are ambiguous and difficult to interpret since none of the relations was statistically significant. Considering the size of the sample ($n = 52$), however, the physiological variation in placental hormones does not seem to affect the components of the glucose tolerance test to any major extent.

Levels of insulin, on the other hand, were explained to a larger extent by the physiological variation in maternal fat mass than by the variation in hPL and all three placental hormones (Table 7). Studies on fat tissue have shown a decrease in numbers of insulin receptors and their sensitivity during pregnancy (Pagano *et al.* 1980; Hjöllund *et al.* 1986). Thus, the amount of fat tissue is an important determinant of the circulating insulin levels in pregnancy, and the increased insulin resistance during late pregnancy may well be associated with a change in insulin receptor function. Most studies on blood tissue (erythrocytes and monocytes), however, found no change in the receptor function during pregnancy (Kühl *et al.* 1984). This might further support the use of fat tissue as a medium for insulin receptor studies when total insulin resistance is the objective of the investigation.

It cannot be inferred from the present study, however, that the increase in insulin resistance (insulin levels) during pregnancy is also related to the amount of maternal fat tissue. For further studies of this question it is necessary to investigate women in early pregnancy and even in the prepregnant state.

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A randomized study of the sitting position for delivery using a newly designed obstetric chair

PETER STEWART, HELEN SPIBY

Summary. A new obstetric chair has been designed to overcome some of the problems of those currently available commercially. The chair has been used to assess the effects of the sitting position in the second stage of labour on the outcome of delivery in 304 women randomly allocated to be delivered either in the chair or in the conventional dorsal position. Delivery in the chair conferred no benefits to mother or baby and resulted in greater mean blood loss and a higher rate of postpartum haemorrhage.

There is considerable evidence to suggest that in primitive societies labour and delivery were conducted in the upright or squatting positions (Englemann 1883). Until a century ago in Europe and North America, the use of a birth chair was common practice (Householder 1974). Since then, however, the recumbent position, either dorsal or left lateral, has been the usual position for delivery. In recent years, some obstetricians and lay people have advocated a return to the modified upright position for delivery, suggesting that it is more physiological and advantageous to the outcome of labour (Howard 1959; Newton & Newton 1960). Although modified delivery beds and specially designed chairs have been described and advocated (Haukeland 1981; Romney 1985; Kesby 1982), most studies of the sitting position for delivery have either involved few patients or have been poorly controlled.

In a randomized study using a birth chair Stewart *et al.* (1983) concluded that the sitting position reduced the use of episiotomies but increased the amount of blood loss at delivery. However, whether or not to perform an episiotomy may well depend more on the judgement of the midwife than on the position of the woman in labour. Also, the design of the chair appeared to cause congestion of the perineum due to herniation of tissues through the seat so that minor trauma of the excessively congested perineum may have been responsible for the increased blood loss found at delivery. Thus it is possible that these two findings reported by Stewart *et al.* (1983) were influenced by the personnel and equipment involved rather than the posture adopted for delivery.

A birth chair has been designed which provides both greater flexibility for the position of the woman during delivery, and also support for the perineum during the second stage of labour, thereby reducing tissue congestion. It seemed appropriate to perform a further randomized study with a different group of midwives, using this new obstetric chair to confirm or refute the previous findings that delivery in the sitting position reduced the use of episiotomy, but increased blood loss.

Patients and methods

The new obstetric chair

The new chair was designed in conjunction with obstetricians from the Medical Research Council Clinical Research Centre at Northwick Park, Harrow, London, and was manufactured

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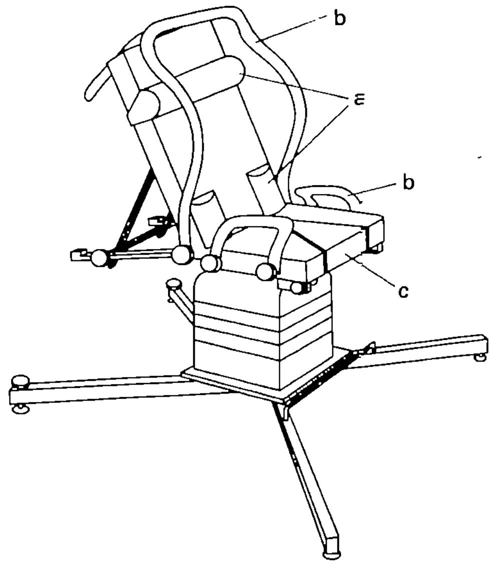

Fig. 1. Design of obstetric chair showing head-rest and side supports (a), hand grabs (b) and the removable portion of the seat (c).

to our specifications by the Rocket Instrument Company of London.

The main features of the chair are illustrated in Fig. 1. A movable head-rest, side- and hand-supports provide comfort for the labouring woman (a and b). Full movements of the chair include a 12° head-down tilt; in case of emergency, the chair can convert to a couch with the insertion of a leg extension. In normal circumstances, there is no hole in the seat of the chair so that maximum support for the perineum is provided up to the time of delivery. A hinged flap (c) can then be opened up to provide good access to the perineum to facilitate control of the delivery by the midwife.

Participants

During a 23-month period from May 1984 to March 1986 all women attending the hospital antenatal clinic during the third trimester were asked to enter the study. Women who were interested had an interview with the research midwife. They were shown the birth chair and given details of the protocol. The use of the chair was restricted to those women who agreed to randomization. The protocol was accepted by the local ethics committee.

The first stage of labour was managed by the labour ward staff in the usual manner. Patients who so desired were ambulant and the fetal heart rate was monitored as considered appropriate. In an attempt to achieve a homogeneous group of 'normal' labouring women, only those with a singleton pregnancy and cephalic presentation who were in spontaneous labour at 37–42 weeks gestation without augmentation or epidural analgesia were included in the study. The women were randomized as late as possible in the first stage in order to reduce to a minimum the number of women who did not successfully enter their intended group. The women were allocated either to delivery in the birth chair or the 'wedged' dorsal position. Allocation was made by opening sealed envelopes.

The chair was maintained in a 15–20° recline from the upright. Fetal well-being in the second stage was assessed in both groups using continuous fetal heart rate monitoring. All deliveries were supervised by a small group of experienced midwives (80% by the research midwife herself) in an attempt to obtain uniformity of technique. No fixed times were allocated for the duration of the second stage and it was allowed to proceed as long as there appeared to be progress with no evidence of maternal or fetal distress. The indications for forceps deliveries and the use of episiotomies were at the discretion of the attending medical and midwifery staff. If vaginal operative intervention was required in those patients in the chair, then they remained in the chair for their delivery.

The total sample size was determined by the 23-month recruitment period.

Data regarding the labour, delivery and condition of the infant were collected, but it was not possible to blind those collecting this information to the experimental group allocation. The 95% confidence intervals (CI) were calculated for differences between means (Armitage 1973) and for relative risks (Freeman 1987).

A subsample of 92 women included in the study were asked their opinion of their delivery position using either an interview schedule or questionnaire dependent on the availability of the research midwife. Following earlier pilot work the interview was standardized to the second day after delivery.

Results

During the 23 months of the study, 980 women were recruited. Of these, 304 fulfilled all the inclusion criteria and were randomized into the

Table 1. Characteristics of the women in the study

Characteristic	Multigravidae Chair (*n*=96)	Multigravidae Bed (*n*=91)	Primigravidae Chair (*n*=61)	Primigravidae Bed (*n*=56)
Height (cm)	160·6 (5·1)	162·5 (5·9)	162·4 (5·3)	162·3 (5·4)
Weight (kg)	72·4 (11·6)	75·6 (11·0)	73·2 (8·9)	71·9 (8·5)
Age (years)	27·8 (4·0)	27·3 (4·4)	24·5 (4·0)	24·8 (4·3)
Gestational age (weeks)	39·7 (1·3)	39·5 (1·1)	39·8 (0·9)	39·8 (1·1)
Socio-economic group				
I	2	6	2	2
II	26	15	14	17
III	42	40	30	24
IV	4	6	3	3
V	0	2	0	1
Unclassified	22	22	12	9

Results are mean (SD) values

two groups for the delivery position. The characteristics of the women in the two groups are shown in Table 1. The differences between the numbers in the groups are accounted for by there being no 'batching' of the randomization envelopes. The study was also terminated at a particular time rather than after a specific number of patients.

The groups were similar in terms of socio-economic class, ethnic origin, mean maternal age, height, weight, gestation at delivery, and attendance at antenatal classes.

Details of the first stage of labour are given in Table 2. The two groups were also similar in the position and station of the fetal head as assessed at full dilatation. Unfortunately, these details were not fully recorded in 32 patients who gave birth in the chair and 43 patients who were delivered in the bed.

Twenty-two patients failed to comply with their intended delivery position. Nineteen of these patients were intended to give birth in the chair: 11 were delivered too quickly to be transferred; three decided that they did not wish to be transferred; two returned to bed as they found the chair uncomfortable; and three were retained in bed for obstetric reasons. Three multiparae who were allocated to be delivered in the semi-recumbent position in bed were then delivered in alternative positions: squatting, kneeling and in the lateral position. The analysis was based on group allocation, that is intention to treat rather than the actual position adopted for delivery.

Details of the second stage of labour and delivery are given in Table 3. Many patients chose to use limited bearing down during the second stage as opposed to organized pushing. There was no difference between the groups in the proportion of women choosing this type of

Table 2. Details of the first stage of labour

First stage of labour	Multigravidae Chair (*n*=96)	Multigravidae Bed (*n*=91)	Primigravidae Chair (*n*=61)	Primigravidae Bed (*n*=56)
Duration (h) mean (SD)	4·7 (2·6)	5·4 (3·1)	7·8 (3·4)	6·8 (3·0)
Ambulation				
Yes	18	19	20	13
No	78	72	40	43
Not recorded	—	—	1	—
Analgesia				
Narcotics	41	35	49	35
Inhalation	34	39	11	18
Nil	21	17	1	3

Table 3. Details of the second stage of labour and delivery

Details	Multigravidae		Primigravidae		All women	
	Chair (*n*=96)	Bed (*n*=91)	Chair (*n*=61)	Bed (*n*=56)	Chair (*n*=157)	Bed (*n*=147)
Duration of second stage (min)						
Mean (SD)	18·8 (14·0)	16·9 (11·6)	70·8 (43·3)	60·9 (46·0)	38·7 (30·0)	33·7 (30·0)
Difference between means (CI)	1·9 (−1·9 to 5·6)		9·2 (−7·1 to 25·5)		5·0 (−3·4 to 13·5)	
Duration of active pushing (min)						
Mean (SD)	16·8 (12·6)	15·9 (11·7)	58·1 (35·0)	52·0 (39·6)	33·0 (24·0)	29·6 (25·0)
Difference between means (CI)	0·9 (−4·5 to 2·6)		6·1 (−7·3 to 19·9)		3·4 (−3·7 to 10·4)	
Mode of delivery						
Spontaneous	96	91	48	48	144	139
Forceps/Ventouse	0	0	13	7	13	7
LSCS	0	0	0	1	0	1
Relative risk (CI)			1·85 (0·68 to 4·99)		1·79 (0·92 to 3·45)	

CI, 95% confidence intervals; LSCS, lower-segment caesarean section.

management of labour. The mean duration of the second stage was similar in women delivered in the bed and in the chair. All multigravidae were delivered spontaneously. One primigravida required a lower-segment caesarean section for suspected cephalopelvic disproportion with an occipito-posterior position. More primigravidae in the chair group required an operative delivery but the difference was not statistically significant.

The neonatal outcome is shown in Table 4. Only one infant (born in the birthing chair) showed signs of neonatal asphyxia with an Apgar score of 3 at 1 min and an umbilical artery pH of 7·29; the baby responded well to resuscitation. The mother had not received any narcotic analgesia.

Blood loss and perineal trauma at delivery are shown in Table 5. Blood loss was significantly increased in the chair delivery group and more women in this group had a postpartum haemorrhage. Fewer episiotomies were performed in the multigravid women in the chair delivery group but this was not apparent in the primigravid women.

From the responses to interview and questionnaire the patients' satisfaction with their allocated delivery position was judged by their experience of comfort in the second stage and preferred delivery position for the next birth. The findings are summarized in Tables 6 and 7. Patients delivered in the chair were more likely to describe their labour as 'comfortable' and none in this group described it as 'very uncomfortable'. All but one patient who had used the chair said they would request it in a

Table 4. Neonatal outcome

Factor	Multigravidae		Primigravidae		All women	
	Chair (*n*=96)	Bed (*n*=91)	Chair (*n*=61)	Bed (*n*=56)	Chair (*n*=157)	Bed (*n*=147)
Birthweight (kg)						
Mean (SD)	3·48 (0·39)	3·59 (0·44)	3·35 (0·32)	3·42 (0·36)	3·43 (0·37)	3·53 (0·42)
Difference between means (CI)	0·11 (−0·27 to 0·49)		0·07 (−0·06 to 0·20)		0·10 (0·01 to 0·19)	
Umbilical artery pH						
Mean (SD)	7·28 (0·09)	7·26 (0·08)	7·23 (0·07)	7·23 (0·07)	7·26 (0·08)	7·25 (0·08)
Difference between means (CI)	0·02 (0·0 to 0·10)				0·01 (−0·02 to 0·10)	
Number with Apgar score <7 at 1 min	6	3	5	3	11	6
Relative risk (CI)	1·95 (−2·31 to 8·84)		1·57 (−2·77 to 6·82)		1·77 (−1·53 to 4·80)	

CI, 95% confidence intervals.

Table 5. Blood loss and perineal trauma at delivery

	Multigravidae		Primigravidae		All Patients	
	Chair (*n*=96)	Bed (*n*=91)	Chair (*n*=61)	Bed (*n*=56)	Chair (*n*=157)	Bed (*n*=147)
Blood loss (ml)						
Mean (SD)	234 (211)	184 (121)	340 (229)	236 (169)	275	204
Difference between means (CI)	50 (−4 to 94)		104 (22 to 186)		71 (26 to 116)	
Postpartum haemorrhage >500 ml	11	3	16	4	27	7
Relative risk (CI)	3·8 (1·0 to 14·2)		4·6 (1·4 to 14·5)		4·1 (1·8 to 9·4)	
Perineal trauma						
None	42	38	17	9	59	47
1st degree tear	19	13	2	12	21	25
Relative risk (CI)	1·5 (0·7 to 3·1)		0·1 (0·0 to 0·6)		0·7 (0·6 to 1·0)	
2nd degree tear	29	25	12	10	41	35
Relative risk (CI)	1·1 (0·6 to 2·2)		1·1 (0·5 to 2·8)		1·1 (0·7 to 1·3)	
Episiotomy	6	15	30	25	36	40
Relative risk (CI)	0·3 (0·2 to 0·7)		1·2 (0·6 to 2·4)		0·8 (0·5 to 1·4)	

CI, 95% confidence intervals.

future delivery. No patient who was delivered in a bed said they would opt for that in the future.

Discussion

Only 282 patients in our study were delivered finally in the trial group to which they were allocated. This reflects the very strict entry criteria which were used so as to obtain a study group of 'normal' patients. We excluded many women who would have been included in other trials.

In 11 of 22 women not delivered in their allocated position, the reason was rapid progress of the second stage of labour. As duration of the second stage was one factor which was being investigated, this group of patients who failed to comply could have altered the overall results. The data were therefore analysed on the basis of 'intention to treat' with the 'failed' patients included, rather than on the actual treatment given. However, a secondary analysis based on the actual position adopted for delivery did not lead to any important modification of the differences and similarities noted in the primary analysis.

The effect of delivery in the chair on perineal trauma remains unresolved. In this study we were unable to confirm a reduction in perineal damage as was reported by Stewart *et al.* (1983). There were fewer episiotomies in the multigravid women in the chair group but this was not reflected in the primigravid women. Turner *et al.* (1986) noted a possible increase in perineal trauma, and Shannahan & Cottrell (1985) stated that in their series 'the majority of deliveries were spontaneous with median episiotomies'. Hemminki *et al.* (1986) also found no significant difference in perineal trauma rate between chair and bed deliveries. Charles White, an 18th century English obstetrician, stated that delivery in the upright position was potentially hazardous 'frequently occasioning laceration of the perineum and sphincter ani' (Atwood 1976), but apart from the study by Turner *et al.* (1986) there seems to be little support for this historical viewpoint. It may well be that this aspect of midwifery is more dependent on individual patients and midwives than on the actual position of delivery.

We have been unable to demonstrate any reduction in the duration of the second stage of

Table 6. Patients' experience of comfort in the second stage

	Delivery position	
	Chair (*n*=52)	Bed (*n*=40)
Comfortable all of the time	23	5
Comfortable part of the time	7	3
Some discomfort part of the time	17	10
Some discomfort all of the time	—	2
Uncomfortable part of the time	—	6
Uncomfortable all of the time	—	4
No response/unclassified	5	10

Table 7. Patients' preference for next delivery related to this delivery

Preferred position for future delivery	Allocated position Chair (n=52)	Allocated position Bed (n=40)
Chair	51	35
Bed	0	0
Alternative position, e.g. kneeling, squatting	1	1
No preference/no response	0	4

labour, or the instrumental delivery rate in women delivered in the chair; indeed our results tend to suggest the opposite. In our series, the rate of forceps delivery may have been so low because women with epidural analgesia were excluded, but Turner *et al.* (1986) found no reduction in their rate of forceps deliveries and they did have an epidural rate of 26%. Also Shannahan & Cottrell (1985) and Hemminki *et al.* (1986) apparently found no significant differences in their rates of instrumental delivery.

There was no obvious benefit to the fetus in terms of Apgar score and umbilical artery pH. A small study by Aarnoudse *et al.* (1984) using a continuous subcutaneous $P\text{O}_2$ electrode had failed to demonstrate any improved oxygenation of the fetus in the upright position.

Three previous studies have concluded that delivery in a birth chair increased the mean blood loss at delivery (Shannahan & Cottrell 1985) or the frequency of postpartum haemorrhage (Turner *et al.* 1986) or both (Stewart *et al.* 1983). The birth chair used in the present trial was specifically designed to provide good support to the perineum and thereby reduce excessive perineal congestion and oedema which has been reported previously (Goodlin & Frederick 1983). This congestion may exacerbate blood loss from perineal lacerations. Despite this, we found a significant increase in mean blood loss in both parity groups with a concomitant increase in postpartum haemorrhage rate. It has been suggested that the greater the blood loss the more it is underestimated (Brant 1967). If that is so, then this potential hazard of delivery in a birth chair may be even greater than our results suggest. The cause of this excessive blood loss remains uncertain. Production of prostaglandin E_2 (PGE_2) (Husslein & Sinzinger 1984) and PGF_2 (Sellers *et al.* 1982) is greatly increased in the third stage of labour and it has been suggested that these may be the hormones primarily responsible for placental separation and preventing haemorrhage from uterine atony. Further work is needed to determine whether posture has any effect on the production of these prostaglandins at the time of delivery.

Interpretation of the results of the interviews and questionnaires concerning satisfaction with delivery position must be undertaken with caution. All participants in the trial could be assumed to be interested in the concept of the birth chair for delivery. It is, therefore, possible that women delivered in the bed responded negatively due to disappointment following randomization.

The experiences of this group of women will be presented in more detail elsewhere but appear to compare with those reported previously by Hillan (1983), who found that the birth chair afforded a more comfortable delivery position, and Hemminki *et al.* (1986) who noted that the chair was the preferred choice of patients for their next delivery.

Having failed to demonstrate any significant obstetric benefits, but clearly shown a possible hazard from delivery in a birth chair, we feel that these facts need to be emphasized to women who request such a delivery.

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Calculating the effectiveness of in-vitro fertilization. A review

HILARY PAGE

Introduction

Health authorities may come under increasing pressure from infertile couples, influenced by media reports of successful treatment, and from gynaecologists who wish to extend the range of treatments available, to provide resources for in-vitro fertilization (IVF).

This article reviews recent estimates of the effectiveness of this treatment and indicates what level of effectiveness is currently being achieved.

To a couple contemplating IVF, or a health authority which must decide whether to fund such a service, the success rate would be regarded as the chance of giving birth, as a result of treatment, among couples accepted by the clinic for treatment, that is the number of maternities per 100 couples treated.

IVF clinics present their results in a variety of ways, some of which are misleading (Soules 1985). Choice of both numerator and denominator is crucial.

The numerator

The outcome of in-vitro fertilization and embryo replacement can be defined in various ways. The following definitions were suggested by Jones *et al.* (1983).

Chemical pregnancy. This is characterized by a brief rise in serum human chorionic gonadotrophin (hCG) level but no delay in the onset of menstruation. The loss of this pregnancy is termed a menstrual miscarriage because it is indistinguishable from normal menstruation. (Where large doses of hCG have been given to induce ovulation, the endogenous hormone may be undetectable until late in the luteal phase, in which case it is not possible to diagnose such a pregnancy.)

A preclinical miscarriage. This occurs when a rise in hCG is sustained after day 11 of the luteal phase, but where menstruation is delayed by not more than 14 days. This early embryo loss should be regarded as a failure of implantation, not a success, although a positive pregnancy test may have been obtained.

A clinical pregnancy. This would be defined as a distinct rise in β-hCG or an ultrasound scan revealing a gestation sac, or both, maintained until at least 28 days after oocyte recovery. These embryo transfers may be regarded as successes (though not always from the patient's point of view); nevertheless, the chance of miscarriage now is still greater than that for naturally occurring pregnancies (Fishel *et al.* 1985).

The Voluntary Licensing Authority for Human In Vitro Fertilisation and Embryology (1987) published data for 1985 from IVF clinics in the UK. Of 481 total number of conceptions 126 (26·2%) were either ectopic pregnancies or ended in miscarriage before 12 weeks. This apparently high rate of miscarriage is not comparable with the rates reported for pregnancies conceived normally. Such pregnancies are not usually confirmed clinically before 6 completed weeks gestation whereas IVF pregnancies are confirmed at 28 days after embryo transfer.

Because of the apparently high rate of miscarriage, success expressed in terms of pregnancies can be misleading. A more informative numerator might be livebirths. However, if the numerator used is *livebirths,* rather than pregnancies, the apparent success rate can be distorted by the proportion of multiple births. In Australia approximately 19% of births after IVF are twin

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births, and 3% are triplet births (Australian IVF Collaborative Group 1986).

For couples embarking on IVF the chances of success are more accurately reflected by the number of maternities resulting in one or more livebirths. A maternity is the event at which a woman becomes a mother: the delivery of a live child.

The denominator

The choice of denominator is even more problematic and varies between one clinic and another.

An editorial in the *British Medical Journal* described the success rate as follows: 'If one pre-embryo is replaced the chances of a pregnancy are about 9·5%; replacing two increases this to 15%, three to 19%, and four or more to 25%' (Richards 1986).

The denominator used here is not the number of couples accepted for treatment, but the number having one, two, three or four embryos replaced. Many couples fail to have one, let alone four, embryos made available for replacement. This denominator is useful in illustrating the increased chance of pregnancy if more than one embryo is replaced, but it is not useful in indicating the overall success of IVF as a treatment for infertility.

Almost all practitioners of IVF use some form of follicular stimulation rather than the natural menstrual cycle, in order to increase the chances of harvesting more than one ovum. Stimulants such as clomiphene citrate and gonadotrophin are used alone or in combination. Some women do not respond satisfactorily to ovarian stimulation: the 'success rate' quoted for IVF is influenced by whether or not the denominator includes cycles in which the follicular response was inadequate.

The optimum time for harvesting ova is predicted by repeated hormonal assay and by observation of the growth of follicles by repeated ultrasound examination. The timing of aspiration is crucial: too early and the ova are not yet 'ripe', too late and spontaneous ovulation may occur with the loss of the ova in the peritoneal cavity. The success rate quoted for IVF will depend on whether the denominator includes cycles in which the harvesting of ova was prevented by spontaneous ovulation, or only those in which harvesting was undertaken, as when success rates are given in which the number of laparoscopies is used as the denominator (Yovich *et al.* 1984).

All cycles which have been initiated should be included. Cancellation, for whatever reason, and at whatever stage in the cycle, should be acknowledged, not disregarded, in the calculation of a success rate.

An indication of the frequency of cancellation at different stages of each cycle of treatment is shown in Table 1 from information published by a private IVF clinic, the Park Clinic, Nottingham (Fishel *et al.* 1986).

It is likely that women in whom early attempts indicated little chance of a successful outcome would be discouraged from seeking further treatment, so an unknown proportion of these 115 cycles may be second or third or subsequent cycles in a group of patients selected for their chance of success.

Per patient or per cycle

A further choice in the matter of denominators is whether to express results per patient or per cycle of treatment.

If more than one cycle of treatment is offered, the overall pregnancy rate per 100 couples

Table 1. Presentation of IVF results, Park Clinic, Nottingham, showing the frequency of cancellation of cycles*

End point of cycle	Number (%)†
Cycle after stimulation	115
Cycle not reaching stage of oocyte recovery	22 (19%)
Cycle with no oocyte recovered	4 (3%)
Cycle with no oocyte fertilized	12 (10%)
Cycle not having embryo replacement for any of above reasons	38 (33%)
Cycle not resulting in pregnancy	91 (79%)

* From Fishel *et al.* (1986).

† Per cent of 115 cycles.

Table 2. Success rates from IVF clinics around the world

	No. of pregnancies	No of couples	Clinical pregnancy rate per 100 couples accepted for treatment (%)
Salt Lake City, USA (Jones *et al.* 1984)	12	100	12
Sendai, Japan (Suzuki *et al.* 1984)	5	72	6·9
Durham, USA (Holman *et al.* 1984)	3	34	8·8
Zagreb, Yugoslavia (Drobjnak *et al.* 1984)	5	157	2·8
Tel-Hashomer, Israel (Dor *et al.* 1984)	5	43	11·6
Miami, USA (Hung & Le Maire 1984)	2	121	1·6
Quebec, Canada (Rioux *et al.* 1984)	0	25	0
Chicago, USA (Scommegna *et al.* 1984)	1	12	8
Houston, USA (Young *et al.* 1984)	1	12	8
Helsinki, Finland (Koskimies *et al.* 1984)	5	57	8·8
Vienna, Austria (Belaisch-Allart *et al.* 1985)	37	321	11·5
Baltimore, USA (Rock *et al.* 1985)	4	23	17
Calgary, Canada (Taylor *et al.* 1985)	9	52	20
Total	89	1029	8·6

accepted for treatment is greater than the pregnancy rate per single cycle of treatment.

The outcome of IVF depends upon the suitability and response of the patient, and on the quality of the technique.

Because these factors may vary from one cycle to the next, failure at the first attempt does not necessarily indicate a poor chance of success at a subsequent attempt. On average, those with the best chance of success become pregnant at the first attempt, leaving a group with a lower chance of success. However, for some patients information gained during the first attempt may enable a second attempt to be undertaken with greater likelihood of success.

It must not be assumed that the pregnancy rate (per 100 couples initially accepted) increases commensurately with the number of cycles of treatment offered. For couples paying for each cycle of treatment, the success rate per cycle is important. It should be stated whether the denominator includes only first cycles, second cycles, etc. or all cycles of treatment, and how patients were selected for second or subsequent cycles.

Where IVF is provided on the National Health Service the number of cycles per couple is usually rationed. Furthermore, many couples will not wish to continue with this stressful treatment after one or two unsuccessful attempts.

Selection of patients

Factors affecting outcome, such as age of the woman, and cause of infertility, may also be taken into account. When counselling individual patients it is appropriate to discuss age-specific and 'infertility cause'-specific success rates. Health care planners will also be interested in success rates for large groups whose distribution of ages and causes of infertility is representative of couples in the population with prolonged infertility, for whom the service might be provided.

Results of IVF

Many IVF clinics have published information about outcome of treatment in the recently launched *Journal of In Vitro Fertilisation and Embryo Transfer.* It was often not possible to deduce from the data given what the success rate would be if expressed as clinical pregnancies per 100 couples embarking on treatment. Table 2 shows the collated information for those units with published data from which this success rate could be deduced.

It is apparent from the small number of patients at most of these units that in these cases the information refers to the inaugural period. Thus the success rates may be expected to improve as more of the initial group of patients undergo further cycles of treatment, and as the practitioners become more experienced and the technique more refined. The average pregnancy rate of all the clinics combined was 8·6%.

More recently, results from two well-established Australian centres have been published for the year 1985 (Rogers *et al.* 1986). In Monash University, the pregnancy rate among 396 couples accepted for treatment was 16·9%. In the Royal Women's Hospital at Melbourne, where 526 couples were accepted for treatment, the pregnancy rate was 10·6%.

The pregnancy rates from IVF are obviously very variable, and large numbers of couples must be treated by a particular clinic, or using a particular technique, before the success rate for that clinic, or for that technique, can be estimated with any degree of certainty.

Looking at the early results worldwide, and at the results from well-established clinics in Australia, it would appear that a pregnancy rate of approximately 10% can be reasonably expected from IVF, and that higher rates of up to approximately 20% can be obtained. These rates obtained on a small series of patients have a large margin of error. The series from Calgary reported by Taylor *et al.* (1985) included 52 couples and nine pregnancies, giving a pregnancy rate of 20% (SE 5·6%, 95% CI 8·8 to 31·2%). However, the SE of the pregnancy rate obtained in the series of 396 couples in Monash (Rogers *et al.* 1986) was much smaller. That series achieved 67 pregnancies giving a pregnancy rate of 16·9% (SE 1·9%, 95%CI 13·1 to 20·7%).

Results in the United Kingdom

The difference between success rates which use pregnancies and maternities as the numerator, and those which use cycles of treatment or couples accepted for treatment as the denominator, can be demonstrated using the aggregate statistics published for all IVF units in the UK by the Voluntary Licensing Authority (1987) (Table 3). Results are published for established centres which started treatment before 1984, and new centres. Clinical pregnancies are those confirmed by ultrasound 28 days after embryo replacement. The distribution of singleton, twin and triplet births resulting from IVF was not given, so the difference between the number of maternities and the number of babies born is not known.

The number of couples treated was fewer than the total number of treatment cycles because many couples had received more than one treatment cycle. Many of the couples not pregnant would undergo further cycles of treatment so that the eventual pregnancy rates and maternity rates per 100 couples treated may be higher than those given here.

Table 3. IVF pregnancy and maternity rates 1985*

	Success rate			
	Per treatment cycle (%)		Per couple treated (%)	
Centre category	Pregnancy rate	Maternity rate	Pregnancy rate	Maternity rate
Established centres	11·6	8·9	14·0	10·6
New centres	9·7	7·1	10·1	7·4
All centres	11·2	8·5	12·9	9·7

* From data published by The Voluntary Licensing Authority for Human In Vitro Fertilisation and Embryology (1987).

Misleading methods of estimating success

Accumulation of cycles of treatment

The fallacy of assuming that the pregnancy rate increases commensurately with the number of cycles of treatment has already been pointed out. Those with the best chance of success are most likely to become pregnant at the first attempt, leaving a group with a lower chance of success. (However, it is still possible to select from this group those with a higher chance of success—see below.)

Life table analysis

A fallacy also occurs when life table analysis is used to estimate the success rates of IVF. In standard life table analysis, such as survival after operation, it is axiomatic that those who are 'lost to follow-up' have the same chance of further survival as those who remain under surveillance. This method of analysis is usually used to follow up a single intervention such as an operation, rather than a series of interventions. When life table analysis is applied to IVF, it is assumed that couples who drop out while still not pregnant would therefore have had the same chance of success as those who remained in the programme. Thus one paper reported a success rate of 70% after eight cycles of treatment (Kovacs & Rogers 1985). In fact those who remain in the programme after two or three cycles are selected for the lack of apparent reason for failure, i.e. among those still not pregnant they have a higher chance of success, compared with those who have left the programme possibly because of a low chance of success.

Meaning of IVF, literal or common usage

The effectiveness of IVF can mean two things. Literally *in vitro* means 'within glass' so that in-vitro fertilization refers to fertilization outside the living body. The effectiveness of this procedure can be viewed simply as the likelihood of fertilization occurring when spermatozoa and ova are put together *in vitro*. By reference to the data in Table 1 it can be seen that 12 cycles out of a possible 89 in which oocytes were obtained resulted in no oocyte being fertilized. Thus the success rate of in-vitro fertilization (taken literally) was 86% (77 of 89).

Since in the fertile population the probability of conception occurring in any one cycle during which sexual intercourse occurs is approximately 25% (Edmonds *et al.* 1982) then it can be said that IVF is more likely than normal intercourse to result in fertilization. This of course is misleading for anyone who wishes to estimate their chance of a pregnancy resulting from the treatment known by common usage as IVF.

All couples who become pregnant?

Among women who conceive after intercourse the probability of conception occurring within three menstrual cycles during which sexual intercourse occurs is approximately 55% (Obel 1980). Among women who become pregnant after IVF the pregnancy rate after three cycles of IVF treatment might also approach 55%, i.e. 55% of those who ever conceive by IVF do so within three cycles of treatment. This has led to a claim that IVF 'approaches a pregnancy rate per cycle which is comparable to the pregnancy rate per month of exposure in normal reproduction' (Jones 1986). This is only true for those who are eventually successful: the proportion who are eventually successful in IVF is small compared to the proportion who are successful in normal reproduction. Thus claims that the pregnancy rate in IVF is equal to that obtained in normal reproduction can be discounted.

Conclusion

There should be standardization of the numerators and denominators used to express the effectiveness of IVF. The number of maternities is considered the most useful numerator. Cycles of treatment or patients accepted for treatment are both useful denominators, and require definition. A cycle of treatment may be defined as any period during which follicular activity (either natural or stimulated) is monitored with a view to harvesting ova. A patient accepted for treatment is one in whom at least one cycle of treatment has been undertaken.

Using these criteria, the success rates achieved by IVF units in the UK are, on average 8·5 maternities per 100 cycles of treatment and 9·7 maternities per 100 couples treated, which will increase somewhat as more women complete the number of attempts they are offered or are prepared to undergo. With improvements in technique the maternity rate may be further increased. However, the effect of case mix is important: success can be maximized by offering treatment to particular groups of patients whose cause of infertility is particularly amenable to IVF. The private sector may wish to concentrate on such patients. University or research departments might undertake the treatment of more difficult cases or couples hitherto thought unsuitable, so that advances in technique may occur without increases in the success rate.

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Induction of abortion in early first trimester human pregnancy using epostane

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Summary. The role of epostane (Sterling Winthrop, Guildford, UK), a competitive inhibitor of the 3β hydroxysteroid dehydrogenase enzyme system (3β-HSD), as an abortifacient agent in early human pregnancy has been studied in 54 women. All were less than 49 days from their last menstrual period. Thirty were treated with 200 mg of epostane every 8 h for 7 days and 24 were given 200 mg every 6 h for 7 days. This caused a sustained reduction in circulating progesterone concentrations, a smaller fall in 17 β-oestradiol and no effect on serum cortisol. Abortion occurred in 21 women (70%) in the lower dosage group and in 20 women (87%) in the higher dosage group. Abortion was incomplete in 6 of these 41 women. A worsening of pregnancy nausea and vomiting was noted by 66% of women in the first group and 84% in the second. There was no delay in the resumption of normal menstruation following abortion. This study confirms the potential of epostane as an effective inhibitor of ovarian and placental steroidogenesis and as a potent abortifacient agent in early human pregnancy.

Progesterone is necessary for the maintenance of human pregnancy. Csapo and Pulkkinen (1978) observed that surgical removal of the corpus luteum (luteectomy) in early pregnancy caused a steep decline in circulating progesterone concentrations which caused bleeding and abortion 3–4 days later. Progesterone replacement after luteectomy maintained the serum progesterone concentration and prevented abortion, while oestrogen supplementation had no effect.

Epostane (Sterling Winthrop, Guildford, UK) is a competitive inhibitor of the 3β hydroxysteroid dehydrogenase enzyme system (3 β-HSD). Animal studies with this compound have shown a preferential ovarian–placental inhibition of steroidogenesis, with minimal adrenal suppression, and an associated abortifacient effect (Creange *et al.* 1981). Early human studies have demonstrated inhibition of ovarian and placental progesterone production, with negligible adrenal effect, but little clinical effect (Pattison *et al.* 1985*a*, *b*). This study examines the effect of prolonged inhibition of progesterone production using higher dose epostane therapy in early human pregnancy.

Patients and methods

Fifty-four healthy women aged between 17 and 41 years gave written informed consent to the study. All were to have termination of pregnancy (within the terms of the Abortion Act, 1967) and were 49 days or less from the first day of their last menstrual period. They were advised that the aim of treatment was to induce an early miscarriage and so avoid a surgical procedure. Women with a clinically significant medical or gynaecological history, or who were

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already on medication or had some contraindication to steroid therapy, were not recruited.

All women had regular menstrual cycles and were certain of the date of their last menstrual period. A general examination was performed to exclude any medical disorder, and a pelvic examination confirmed that the uterine size was compatible with the calculated gestation. Pregnancy was confirmed with a urinary β-hCG assay (Beta Clone, Monoclonal Antibodies, Inc., High Wycombe, UK).

The women were assigned consecutively to two treatment groups. The first 30 women were treated with 200 mg of epostane every 8 h for 7 days and the remaining 24 with 200 mg of epostane every 6 h for 7 days. All the women were seen at 1, 2 and 6 weeks after treatment and the clinical outcome was assessed on the patient's history, a vaginal examination and a urinary pregnancy test. Surgical termination of pregnancy was arranged without delay in the event of treatment failure.

Two blood samples, collected 30 min apart, were taken before the start of epostane treatment. Further samples were taken on days 2, 3, 5, 7, 8 and 14 of the study, at variable times during the day. The samples were allowed to clot at room temperature and serum was separated and stored in aliquot samples at −20°C until assayed. Serum progesterone, 17β-oestradiol and cortisol were measured in all samples. A full blood count, liver function tests, urea, creatinine and electrolyte estimation were performed before and after each treatment course. Progesterone, oestradiol and cortisol were measured by radioimmunoassay (RIA) using methods described previously (Pattison *et al.* 1985*a*).

The hospital ethics committee approved this study.

Statistical methods. The mean (SE) was calculated for each time point in the study. The results were compared using Student's *t*-test.

Results

Clinical effect

Patient details and clinical outcome for each group are shown in Table 1. In the first group, treated with 600 mg of epostane per day, 21 of the 30 patients (70%) aborted and the abortion was complete in 17 (80%) of these women. Surgical evacuation of retained products of conception was necessary in four women. Six of the remaining nine women experienced some bleeding, which settled after stopping treatment, and all nine women required surgical termination of pregnancy. There were no statistically significant differences in gestation, age or parity between those who aborted and those with a continuing pregnancy. Bleeding started between days 5 and 6 of treatment and persisted for between 9 and 10 days. The initial loss was usually heavy, lasting 3–12 h, and was followed by a menstrual-type loss.

There were four treatment failures in the group of 24 women treated with 800 mg of epostane per day. Steroid hormone measurements suggest that one of these women stopped taking epostane with the onset of bleeding, and she has therefore been excluded from the analysis. Of the 23 other patients in this group 20 aborted (87%) and abortion was complete in 18 (90%) and incomplete in two, both of whom underwent curettage. Two of the four patients with a continuing pregnancy at follow-up had shown signs of threatened abortion, which stopped after treatment, and all four underwent surgical termination of pregnancy. The onset

Table 1. Clinical outcome in two treatment groups

	Epostane treatment	
Characteristics	600 mg/day ($n = 30$)	800 mg/day ($n = 24$)
Maternal age (years) mean (SD)	26·8 (7·7)	25·5 (6·2)
Gestation (days) mean (SD)	44·4 (4·8)	43·9 (4·5)
Nulliparous (*n*)	18	14
Abortion (*n*)	21	20
Complete abortion (*n*)	17	18
Continuing pregnancy (*n*)	9	4
Threatened abortion (*n*)	6	2

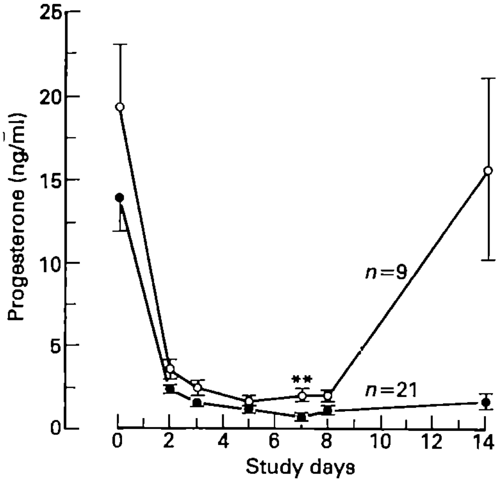

Fig. 1. Serum progesterone concentrations in women treated with epostane, 600 mg/day for 7 days, comparing the group who aborted (●) with the continuing pregnancy group (○). **$P<0{\cdot}1$

and duration of bleeding was similar to that seen in the first group except that one patient experienced prolonged heavy bleeding for 24 h, when miscarriage occurred at 49 days gestation. This bleeding settled spontaneously, but a post-treatment haemoglobin estimation was 10·2 g/dl (13·7 g/dl before treatment) and the patient was treated with iron.

When abortion occurred in the first 10 days after the missed period, the bleeding consisted of a menstrual-type loss with little discomfort. The amount of bleeding generally increased with increasing gestation, and heavy bleeding was frequently associated with cramping lower abdominal pain which was satisfactorily relieved in all women with oral analgesics. Of the 54 women in the study 34 (62%) were between 43 and 49 days gestation at the start of treatment.

All women had resumed normal menstruation within 6 weeks of induction of abortion.

Side-effects

Of the 30 women treated with 600 mg/day, 20 (66%) complained of some side-effect. The most common complaint was a worsening of pregnancy nausea in 18 women. Twelve of these women also complained of at least one episode of vomiting and five noted occasional dizziness.

In the 800 mg per day group, 21 of the 24 women (87%) complained of some side-effect. Nausea occurred in 20 women, vomiting in 12 and dizziness in six. An oral anti-emetic (metoclopramide, 10 mg every 8 h) was given to those complaining of nausea or vomiting, with a general improvement in the level of side-effect. Despite this high frequency of side-effects most women were able to continue with their normal daily activities and they expressed satisfaction with the method of treatment.

Steroid hormones

Serum progesterone concentrations fell, after starting epostane treatment, to 5% of the pretreatment value and remained low for the duration of the course. In the 600 mg/day group there were significant differences in progesterone concentrations between the women who aborted and those with a continuing pregnancy, at 7 ($P<0{\cdot}01$) and 14 ($P<0{\cdot}05$) days (Fig. 1). In the 800 mg/day group, progesterone concentrations declined to significantly lower values in the women who aborted than in those with continuing pregnancy (Fig. 2). In one patient from this group the progesterone concentration had returned to the pretreatment value by day 7, suggesting she had stopped treatment on day 5 or 6 which coincided with the time of onset of bleeding.

There was a smaller fall in oestradiol concentrations to 25% of the pretreatment value. In the 600 mg/day group there were significant

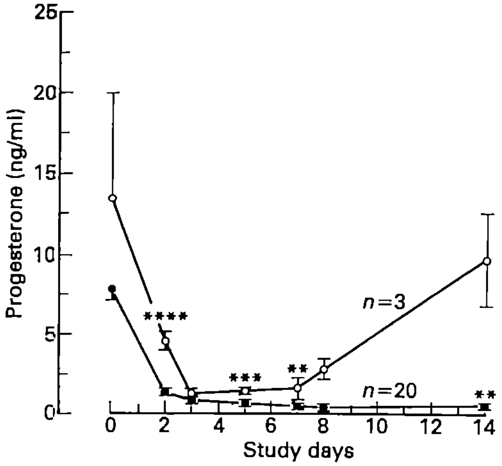

Fig. 2. Serum progesterone concentrations in a group of women treated with epostane, 800 mg/day for 7 days, comparing the group who aborted (●) with the continuing pregnancy group (○). **$P<0{\cdot}01$, ***$P<0{\cdot}001$, ****$P<0{\cdot}0001$.

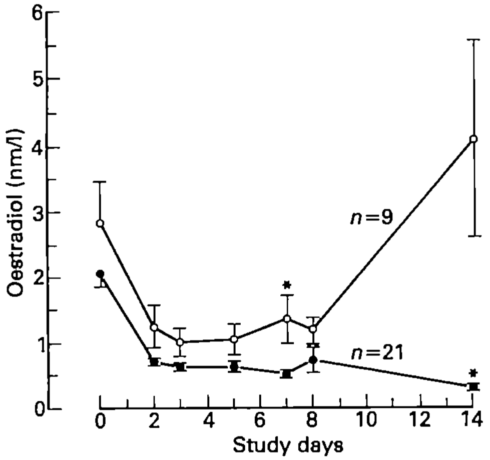

Fig. 3. Serum oestradiol concentrations in a group of women treated with epostane, 600 mg/day for 7 days, comparing the group who aborted (●) with the continuing pregnancy group (○). *$P<0{\cdot}05$.

differences in oestradiol concentrations between those women who aborted and those with continuing pregnancy at 7 ($P<0{\cdot}05$) and 14 ($P<0{\cdot}05$) days (Fig. 3). In the 800 mg/day group the treatment failures had significantly higher oestradiol concentrations than the women who aborted (Fig. 4). In one patient there was a rise on day 7 to the pretreatment level, consistent with the change in progesterone concentration.

Serum cortisol concentrations remained within the normal range throughout treatment at both dose regimens. There was an unexpected rise of cortisol concentrations on days 2 ($P<0{\cdot}001$) and 3 ($P<0{\cdot}01$), when compared with the pretreatment values, in the 600 mg/day group (Fig. 5).

Haematology and biochemistry

The haematology and biochemistry measurements remained within the normal range after treatment.

Discussion

This study confirms that early human pregnancy can be disrupted by inhibition of the ovarian and placental 3β-HSD enzyme system which causes suppression of circulating progesterone and oestrogen concentrations and supports the hypothesis of a progesterone myometrial block during pregnancy.

In the group of women treated with 600 mg/day there were significant differences in the progesterone concentrations between those who aborted and those with continuing pregnancy. The continuing pregnancy rate of 30% may have been due to insufficient inhibition of progesterone production and failure to reach the threshold level at which abortion will ensue. At the higher dose of 800 mg/day the failure rate was only 13% and again these women had significantly higher progesterone concentrations when compared with the group that aborted.

Other studies have reported similar abortion rates in women treated with 800 mg of epostane per day. Birgerson *et al.* (1986) treated 10 pregnant women (41–59 days from LMP) with 800 mg/day for 4 days, and abortion occurred in 8 of the 10 patients (80%) and was judged complete in five. In a larger Dutch series, 50 pregnant women (< 8 weeks from LMP) were treated with 800 mg/day for 7 days and 42 (84%) aborted (Crooij *et al.* 1987). Abortion was incomplete in two women and eight failed to respond to the treatment. The women who failed to respond did not show a significant fall in progesterone concentration by day 7 of treatment, compared with the pretreatment value.

The suggestion that there may be a critical level of progesterone necessary for the maintenance of human pregnancy was first put forward

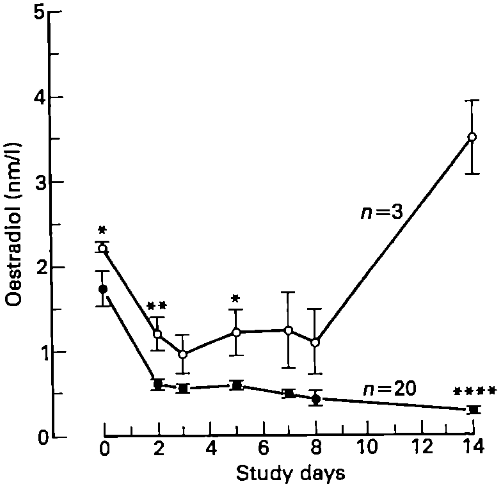

Fig. 4. Serum oestradiol concentrations in a group of women treated with epostane, 800 mg/day for 7 days, comparing the group who aborted (●) with the continuing pregnancy group (○). *$P<0{\cdot}05$, **$P<0{\cdot}01$, ****$P<0{\cdot}0001$.

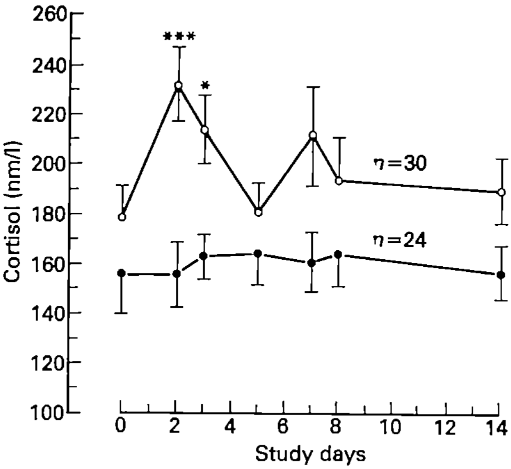

Fig. 5. Serum cortisol concentrations in women treated with epostane, 600 mg/day for 7 days (○) and 800 mg/day for 7 days (●). In the 600 mg/day group there were significant differences between the pretreatment value and the values during treatment: $^{*}P<0{\cdot}05$, $^{***}P<0{\cdot}0001$

by Csapo (1975) and Csapo & Pulkkinen (1978). On the basis of luteectomy studies, it was suggested that the critical level for progesterone was 12 nmol/l (4 ng/ml) and that below this abortion occurred after 3–4 days. Assuming that the assay used in our study and that used by Csapo are comparable, our results suggest a lower threshold value of 3–6 nmol/l (1–2 ng/ml).

The higher abortion rate in the higher dose group may simply be a dose response effect. Alternatively, it may be due to a more constant inhibition of 3β-HSD with elimination of the fluctuations in hormone level that may occur, particularly at the cellular level, with episodic drug administration. In a 24-h study, Pattison *et al.* (1985*a*) showed a fluctuating peripheral progesterone concentration with a dose of 100 mg of epostane every 8 h whereas a 100-mg dose every 6 h gave a more constant inhibition. This is consistent with the short 90-min half-life of the drug and could account for some of the treatment failures which may be eliminated with a drug delivery system that produces a constant drug blood level with minimal fluctuation (M. A. Webster, unpublished observation).

Serum cortisol concentrations remained within the normal range in all women treated with epostane. This supports the concept of a preferential ovarian/placental effect of this compound that was first noted in the animal studies and in the early human trials (Creange *et al.* 1981; Pattison *et al.* 1985*a, b*). Although it was not possible for the patients to attend for blood sampling at the same time each day, the pretreatment sample was always collected before 11.00 hours and the treatment samples were taken either at the same time or later in the day when they would be expected to be lower because of the normal diurnal variation. It has been suggested by Van Der Spuy *et al.* (1983) that cortisol concentrations may be maintained by the long loop negative feedback of ACTH on the adrenal gland. This requires further investigation.

Nausea and vomiting were the most common side-effects, affecting 66% and 83% of patients in the low- and high-dose groups, respectively. This appeared to be due to a worsening of the nausea of pregnancy as these side-effects have not been a problem in non-pregnant women or in men. Some relief was obtained from an oral anti-emetic, and most women found that the side-effects were tolerable, with little disruption of their usual daily activities.

It is interesting to compare the epostane results with another anti-progesterone compound, RU 486 (mifepristone), which acts as a competitive inhibitor of progesterone at the receptor level. Initial studies with this drug showed abortion rates of 82% (Herrman *et al.* 1982), and later studies with larger series confirmed rates of 85–90% (Kovacs *et al.* 1984; Couzinet *et al.* 1986). The abortion rates for both drugs are similar, despite their different modes of action to achieve an anti-progesterone effect. The 10–15% failure rate for both compounds suggests that there may be some other factor responsible for the maintenance of pregnancy, yet to be identified. To test the progesterone hypothesis further it would be useful to combine these two compounds to produce a maximal antiprogesterone effect. Both compounds have been shown to sensitize the myometrium to small amounts of exogenous prostaglandin (PG) and this may be useful for the management of the small number of treatment failures (Bygdeman and Swahn 1985; Webster *et al.* 1985).

There is a need for a safe, reliable agent for the termination of early pregnancy. Prostaglandins have been extensively investigated and found to be unsuitable because of pain and gastrointestinal side-effects. Other 3β-HSD inhibitors have been examined and rejected because of either poor results or unacceptable adrenal or hepatic effects. The original intention in our trial was to restrict treatment to the first 7 to 10 days after the missed period and so induce a menstrual-type bleed. However, because of late referral of patients, the limit was extended to 7 weeks from the last menstrual period. The problems with induction of abortion at this later gestation include excessive bleeding, pain and retained products of conception requiring surgical evacuation. All of these were seen in this study and we do not recommend epostane therapy as a replacement for surgical termination. Ideally, it should be given in the first week after the missed period for induction of an uncomplicated uterine bleed.

In conclusion, this study confirms the potential of epostane as an inhibitor of ovarian and placental steroidogenesis and as an abortifacient agent in early human pregnancy.

Acknowledgments

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Absorption of irrigating fluid during laser photocoagulation of the endometrium in the treatment of menorrhagia

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Summary. Twelve women undergoing laser ablation of the uterus for menorrhagia were studied by haemodynamic, biochemical and haematological indices including radioisotope dilution studies of plasma volume to assess the degree of fluid absorption into the circulation during laser surgery. There was a significant rise in central venous pressure and serum chloride and a significant decrease in plasma protein, albumin and haematocrit. Absorption of the irrigating fluid used was demonstrated and in one woman whose case history is illustrated this was excessive.

Laser photovaporization of the endometrium to treat severe menorrhagia was first described by Goldrath *et al.* (1981) in Detroit using a Neodymium YAG laser. During this treatment the uterus is continuously flushed with a suitable irrigating fluid to maintain visibility through the hysteroscope and to remove blood and debris. Photovaporization and photocoagulation are performed under direct vision with the laser directed at the endometrium via an optical fibre. This has proved to be an effective alternative treatment for menorrhagia and is likely to be increasingly used (Goldrath 1986).

One problem found previously with this procedure is occasional excessive fluid absorption causing tissue oedema and a marked diuresis postoperatively (Goldrath 1986). This phenomenon is thought to be similar to the excessive absorption of fluid through open venous sinuses which may occur during transurethral prostatectomy (Mebust *et al.* 1970) which can lead to cardiac failure and pulmonary oedema and is potentially lethal.

It was decided to determine the degree of fluid absorption during laser photovaporization of the endometrium using both clinical and laboratory measurements including radioisotope dilution studies and to ascertain the minimum safe level of cardiovascular monitoring required to detect and treat this phenomenon if it occurs.

Patients and methods

Ethical approval was obtained for the study and all women recruited gave informed written consent. The study included 12 premenopausal women, mean age 42 years (SD 6·9) who presented at the gynaecology clinic, between January and September 1986, complaining of menorrhagia, with no other gynaecological abnormality and no major systemic disease.

On the day of operation the patients were fasted and given a premedication of 15 mg of papaveretum and 0·3 mg of scopalamine intramuscularly. They were also given 60 mg of potassium iodide orally to prevent uptake of radioisotope into the thyroid gland. Blood was withdrawn to determine serum osmolality, urea,

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electrolytes, albumin, total protein, haemoglobin and packed cell volume.

Just before the procedure, venous access was established and 0·2 MBq of ^{125}I-labelled human serum albumin (hSA) was injected intravenously in order to estimate the plasma volume (International Committee for Standardization in Haematology 1980). Anaesthesia was induced with thiopentone (5 mg/kg), and alcuronium (0·6 mg/kg) was given to obtain muscle relaxation. A cuffed endotracheal tube was passed into the patient's trachea, and anaesthesia was maintained by ventilating with a nitrous oxide, oxygen and isoflurane mixture using a tidal volume of 10 ml/kg and respiratory rate of 12–18 breaths/min.

Allen's test was used to confirm collateral circulation through the ulnar artery then an arterial line was inserted via the radial artery in order to facilitate blood sampling and blood pressure monitoring. A central venous pressure line was inserted either via the right subclavian or internal jugular vein to monitor central venous pressure (CVP).

Arterial blood pressure, pulse and CVP were monitored and recorded by the author at 10- or 15-min intervals from induction until 30 min after the procedure was completed and thereafter hourly overnight by the nursing staff. Blood samples were withdrawn into lithium heparin tubes at 10-min intervals for 30 min from the time of injection of the ^{125}I-labelled hSA and then at 15–20-min intervals thereafter until the procedure was concluded. At this point 2 MBq of ^{99}Tc-labelled hSA were injected and blood samples were withdrawn at 10-min intervals for a further 30 min to determine the change in plasma volume. The actual technique of laser ablation has been described previously (Davis 1987).

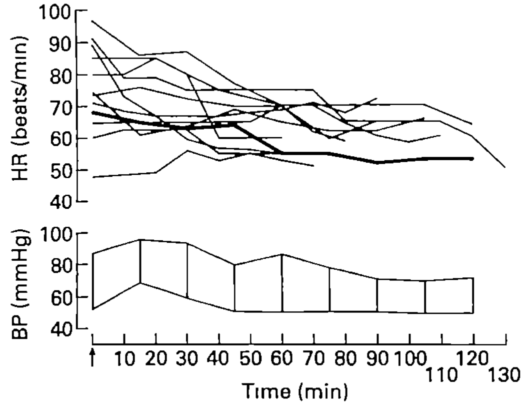

Fig. 1. Upper part shows heart rate (HR) measurements throughout the procedure for each patient. Values for patient no 11 are indicated by the bold line. Lower part shows blood pressure (BP) changes, i.e. the mean of the systolic and diastolic blood pressure for the 12 women at each point in time throughout the procedure.

An electric roller pump was used to irrigate the uterus during the procedure with a measured volume of either 0·9% saline in 5% dextrose or 0·9% saline (the first three patients were irrigated with 0·9% saline in 5% dextrose but when this was no longer available the next nine patients were irrigated with 0·9% saline). During laser treatment the gynaecologist determined the rate of infusion of the fluid into the uterus from 0 to 400 ml/min depending on the clarity of the operating field of vision. Fluid returned from the uterus was collected and measured. During the procedure the patient received only enough fluid intravenously to keep the central line patent. A urinary catheter was inserted at the conclusion of the procedure and urinary output was measured hourly for 16 h.

The blood samples collected during the procedure were analysed to measure plasma volume. A further sample was obtained at the end of the procedure, 4 h and 16 h later to measure the same variables as assessed before operation. The blood samples were all analysed in the biochemistry, haematology and nuclear medicine laboratories of Stobhill General Hospital.

Five patients undergoing hysterectomy were recruited to act as controls in the analysis of the plasma volume changes. They received the same injections of ^{125}I- and ^{99}Tc-labelled hSA and similar anaesthetic management as the study patients but were otherwise independent of the study.

Results

The mean duration of laser ablation treatment was 92 min (range 50–120 min). The mean volume of fluid used to irrigate the uterus was 15·8 litres (SD 7·86). The mean volume of fluid collected from the uterus was 13·3 litres (SD 8·48). The mean fluid intake intravenously and orally from the end of the procedure until 16 h later was 1460 ml (SD 474) and the mean urine output during the same period of time was 1618 ml (range 577–8120 ml).

The blood pressure and pulse rate did not alter significantly during the procedure (Fig. 1). How-

Table 1. Changes in biochemical and haematological indices during laser surgery in 12 patients

Factor	Before operation	Time after operation 0	4 h	16 h
Serum chloride (mmol/l)	105 (3)	109 (5)	107 (4)	104 (3)
Serum protein (g/l)	64·6 (5·3)	54·4 (7·2)	55·3 (4·2)	55 (4)
Serum albumin (g/l)	39·3 (2·8)	33·4 (4·4)	33·8 (2·5)	33·4 (2·3)
Serum osmolality (mosmol/kg)	283 (4)	286 (5)	282 (5)	277 (4)
Serum urea (mmol/l)	4·1 (1·1)	3·9 (1·4)	4·1 (1·7)	3·6 (1·3)
Serum creatinine (μmol/l)	92 (13)	87 (18)	86 (16)	84 (9)
Haematocrit (%)	41·9 (3·1)	35·7 (4·4)	—	38·2 (3·5)

Results are mean (SD) values.

ever, the CVP rose in all patients and the rise was marked in five patients, especially patient no. 11 (Fig. 2). The mean maximum rise was 6·6 cm H_2O (confidence interval (CI) 2·1 to 11·1). Patient no. 11 demonstrated extreme fluid overload and her case history is presented later.

There was a significant rise in serum chloride (mean 4·3 mmol/l, CI 1·9 to 6·6) (Fig. 3) immediately after operation and a significant decrease in serum protein (mean 10·2 g/l, CI 7·3 to 13·1) and serum albumin concentrations (Fig. 4) and also in haematocrit (mean 6·2%, CI 3·0 to 9·5) (Fig. 5). Of these, only the serum chloride had returned to the baseline value by the following morning (mean 6·6 mmol/l, CI 3·2 to 9·95) (Table 1). These results were analysed by Student's paired *t*-test with Bonferoni's correction to allow for multiple comparisons.

There was no change in the serum osmolality during the procedure but the values were significantly lower than baseline on the following morning (mean 6·6 mmol/l, CI 3·2 to 9·95) (Fig. 6).

There was no significant change in the serum urea or creatinine (P>0·05). None of the changes was correlated with the age of the patient or duration of the procedure.

According to the concentrations of radioactivity measured there was a mean rise in plasma volume during the procedure of 0·4 litres (SD 0·55). However, the mean change in plasma volume in the control group undergoing hysterectomy was 0·3 litres (SD 0·42), so that the rise in plasma volume in the laser treatment group is not significant (P>0·05). In some of the laser treated patients, there was an indication from the changes in the radioactivity level in the intermediate samples during the procedure that the plasma volume had increased transiently. However, the level was changing so quickly in the plasma that our sampling interval was unable to detect the absolute increase although extrapolation suggested that in some there had been a transiently large increase in the plasma volume which had fallen to a lower value by the time the sample was taken.

Case report of patient no. 11

The patient was a 35-year-old woman with no significant features in her past medical history

Table 2. Changes in biochemical and haematological indices in patient no. 11

Factor	Before operation	Time after operation 0	4 h	16 h
Serum chloride (mmol/l)	105	118	111	103
Serum protein (g/l)	71	54	53	57
Serum albumin (g/l)	40	31	31	33
Serum osmolality (mosmol/kg)	279	293	283	278
Serum urea (mmol/l)	2·7	2·2	2·1	2·1
Haematocrit (%)	43·4	37·8	—	—
Haemoglobin (g/dl)	14·1	12·8	—	—

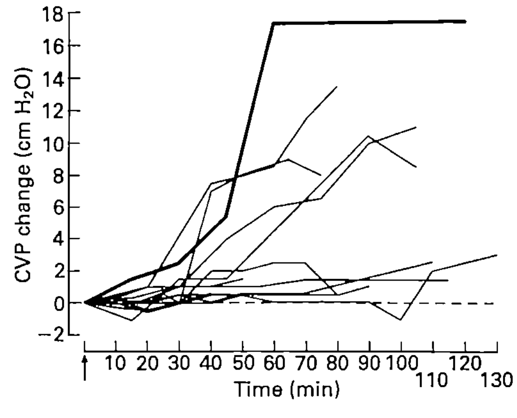

Fig. 2. Central venous pressure (CVP) measurements throughout the procedure for each patient. Values for patient no. 11 are indicated by the bold line.

and she was prepared in exactly the same way as the other patients.

Fifteen minutes after the start of irrigation her CVP was noted to have risen by 2 cm H_2O above the baseline level recorded before the start of the procedure. The CVP continued to rise over the next 45 min until it reached 18 cm above the baseline. During the next hour she gradually developed oedema of her upper body and arms with marked peri-orbital oedema. She was given 40 mg of frusemide intravenously and the procedure was terminated.

During reversal of anaesthesia with 2·5 mg of neostigmine and 1·2 mg of atropine some bronchospasm was noted and as her conscious level improved she was found to be extremely confused. During the evening her clinical condition quickly improved without further diuretic and she suffered no ill-effects from this complication. The change in her cardiovascular status was most dramatically reflected by the change in CVP (Fig. 7). Both pulse and blood pressure decreased although these changes would not have aroused clinical suspicion of fluid overload. The change in plasma volume also indicates the fluid absorption which occurred.

In addition, biochemical variables and haematological indices also reflect the excessive fluid absorption of saline (Table 2). There was a striking discrepancy between the volume of fluid used in irrigating the uterus and the volume collected and measured after the procedure and this was reflected in the massive diuresis which occurred overnight after the operation (Table 3).

There is no doubt that this patient suffered excessive fluid absorption detected both clinically and by objective measurement and the only possible route of this fluid absorption was across the endometrium.

Discussion

In a series of 260 patients, Goldrath (1986) found evidence of fluid overload in several. These patients had some facial oedema and a marked diuresis during the first 24 h after operation. In one of his patients, irrigated with 5% dextrose, dilutional hyponatraemia was found immediately after the operation and it corrected spontaneously. Two patients developed pulmonary oedema when the amount of fluid they absorbed was underestimated but they both responded well to conservative therapy. The phenomenon of excessive fluid absorption during this procedure may be compared to the transurethral resection syndrome which is due to absorption into the circulation of a large volume of electrolyte-free irrigating solution (1·5% glycine) via sinuses in the prostatic fossa during prostatic resection. The symptoms vary from restlessness to convulsions and signs of pulmonary oedema (Sellevold *et al.* 1983). As much as 8 litres of fluid can be introduced into the circulation during this procedure (Emmett *et al.* 1969).

Three distinct abnormalities are associated with the transurethral resection syndrome: hypervolaemia, a decrease in colloid osmotic pressure, and hyponatraemia. It has been suggested that if a completely physiological solution

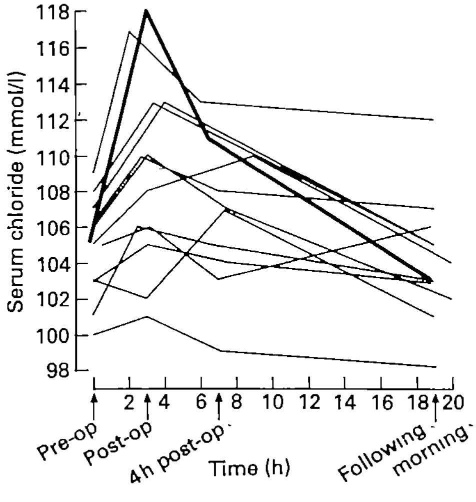

Fig. 3. Serum chloride measured before operation and again at 0, 4 and 16 h after operation. Values for patient no 11 indicated by bold line.

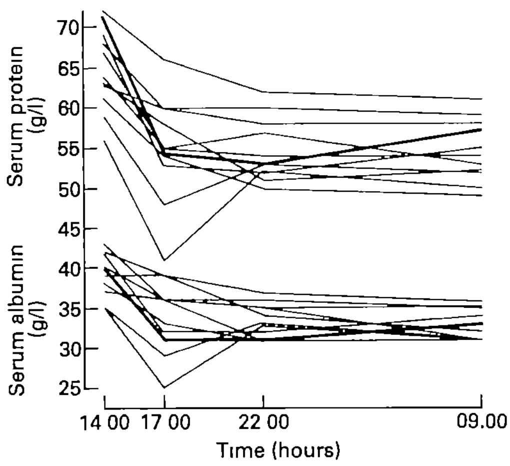

Fig. 4. Serum protein and albumin measured before operation and again at 0, 4 and 16 h after operation for 11 patients (the measurements were incomplete for one patient). Values for patient no 11 indicated by bold line.

could be used in this procedure then this syndrome could be virtually eliminated. However, the use of diathermy for resection prevents the use of electrolyte solutions for irrigation. For the laser ablations in our study either 0·9% saline in 5% dextrose or 0·9% saline was used for irrigation and therefore hyponatraemia was not a problem. Excess fluid absorption, however, still occurred. This was detected by the gross difference between the volume of irrigating fluid and fluid collected leaving the uterus as well as by the biochemical and haematological indices and CVP changes

Patient no. 11 would appear to have absorbed most of the 10 litres of fluid which represented the discrepancy between the volume of fluid used to irrigate the uterus and the volume collected at the end of the procedure. Although a small volume of fluid may have been lost by spillage (and this was not reported as being excessive), the obvious clinical changes and the enormous diuresis which occurred overnight suggest that this patient did absorb as much as 8–10 litres of irrigating solution. Fortunately she suffered no ill-effects, but in an older, less fit patient this may not have been the case. This patient was able quickly to redistribute the fluid she was absorbing into the interstitial fluid space as demonstrated by the rapidly developing oedema. The rapid redistribution of fluid (Thomson 1983; Twigley & Hillman 1985) explains the decline in plasma volume expansion which occurred with time, after an initial increase, as suggested by the radioisotope values (Fig. 7).

The explanations put forward for excessive fluid absorption occurring during laser ablation include insufficient dilatation of the cervix. Goldrath (1986) suggested that the cervix must be dilated sufficiently to allow free fluid flow from the uterus around the hysteroscope or excessive fluid absorption might occur. In our study the cervix was dilated to not less than 9 mm diameter in each patient. The hysteroscope used measured 8 mm in diameter and so free flow of irrigating solution around the hysteroscope was presumed to be assured. Hence we can neither refute nor support the theory of inadequate dilatation.

Goldrath (1986) also suggested that if the procedure were prolonged then excessive fluid absorption might occur. The duration of the procedure in patient no. 11 was no longer than any other and the first signs of fluid absorption occurred after only 15 min of irrigation. In addition the duration of the procedure was not correlated significantly with rise in CVP, rise in serum

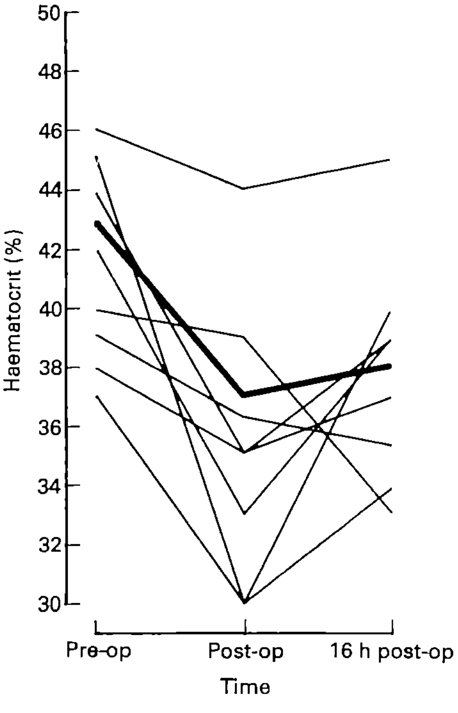

Fig. 5. Haematocrit measured before operation and again at 0, 4 and 16 h after operation. Values for patient no 11 indicated by bold line.

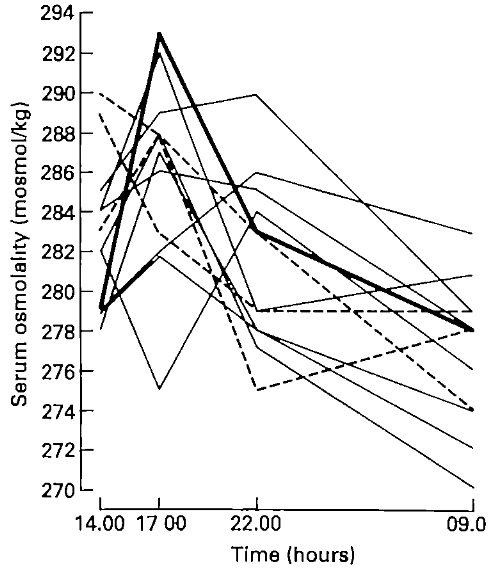

Fig. 6. Serum osmolality measured before operation and again at 0, 4 and 16 h after operation. The first three patients (broken lines) were irrigated with 0·9% saline in 5% dextrose, and the last nine patients (solid lines) were irrigated with 0·9% saline. Patient no.11 is indicated by the bold line.

chloride, fall in serum protein and serum albumin or fall in haematocrit.

It has also been suggested that if the uterine tubes were not occluded then excessive fluid could pass through them into the peritoneal cavity and be absorbed subsequently into the circulation. Not all the patients in our study had occluded uterine tubes but patient no.11 had had her tubes occluded by a previous laparoscopic sterilization. In our study, the amount of fluid absorbed was not affected by tubal occlusion, a finding confirmed by Lomano (1986).

It has been suggested that maintaining the pressure head of irrigating fluid below 60 cm of water during transurethral resection will reduce excessive fluid absorption (Mitchell 1981). In our study the rate of infusion of irrigating fluid ranged from 0 to 400 ml/min and was determined by the operator in order to keep the field of vision clear. It was not possible to keep a record of the rate of infusion in each woman at any one time so it is conceivable that a short-term but excessive increase in the rate of irrigation at any one point may have produced a head of pressure sufficient to increase the rate of absorption of fluid across the endometrium. However, the average rate of irrigation of fluid calculated by dividing the total volume of fluid used by the duration of the procedure was 173 ml/min (range 72–314 ml/min). Patient no.11 had an average rate of infusion of 138 ml/min and so this possible explanation seems rather less likely.

Although a higher level of laser power will more effectively destroy and vaporize the endometrium, it may at the same time open up blood vessels and possibly increase the quantity of fluid entering the circulation. The Neodymium-YAG laser utilizes high energy levels and this may be a contributory factor in allowing excess fluid absorption across the endometrium.

The second aim of the study was to assess the minimum amount of cardiovascular monitoring required to detect excessive fluid absorption quickly. We were satisfied that the most reliable method was by monitoring CVP changes. Blood pressure and pulse measurement were both inaccurate methods of estimating fluid changes and although several of the laboratory measurements detected the fluid volume changes, these would not be available during the procedure. As shown previously, elevation of CVP is the most sensitive indication of rapid absorption of irrigating fluid during transurethral resection of the prostate (Mebust *et al.* 1970). In addition the blood pressure and pulse rate did not reflect the true clinical situation in many cases.

In conclusion, because of the small size of this study we do not know how frequently excessive fluid absorption will occur during this procedure but we have demonstrated that it can occur and that steps must be taken to ensure that it is detected quickly and treated to prevent potentially dangerous consequences. The best method of achieving this is by central venous pressure monitoring and we suggest that this should be performed particularly on patients selected for laser ablation who are less fit or have a history of cardiovascular disease. Why excessive fluid absorption occurred to a dramatic extent in only one patient studied is not fully explained and further work is required to elicit fully the mechanism behind this phenomenon.

Table 3. Fluid balance in patient no. 11

Amount of fluid used in irrigation (ml)	16 500
Amount of fluid collected and measured (ml)	6000
Discrepancy (ml)	10 500
Oral and intravenous fluid overnight (ml)	500
Urine passed overnight (ml)	8100

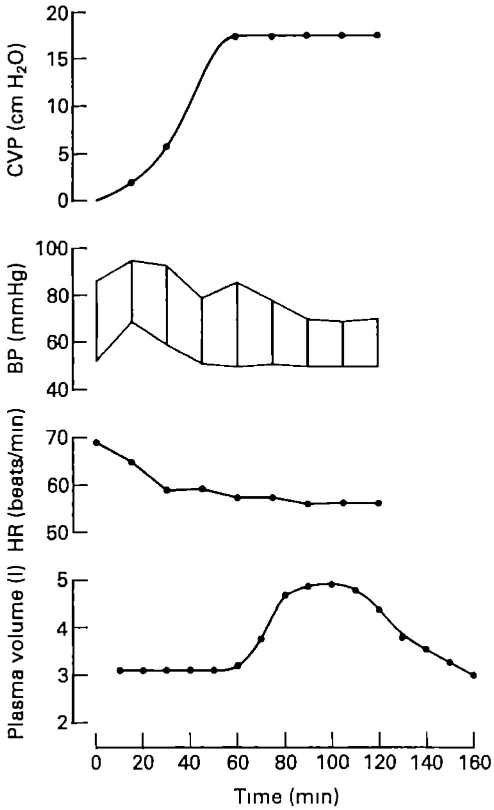

Fig. 7. Changes in central venous pressure, blood pressure, heart rate and plasma volume in patient no.11 during the procedure.

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The role of postoperative alkylating agent therapy in early-stage epithelial ovarian cancer

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Summary. Forty-six patients with early (Stage I and II) ovarian cancer referred as free of residual disease after primary surgery, selected for high-risk features, were treated with adjuvant single-agent alkylating therapy comprising either intravenous cyclophosphamide (1 g/m^2) in 36 patients, or oral melphalan (0·2 mg/kg daily for 5 days) in eight. Cyclophosphamide was repeated every 3 weeks for 10 cycles and melphalan every 6 weeks for 12 cycles. With a median follow-up of 36+ months, 18 patients have relapsed. The actuarial 5-year relapse-free survival was 48% and the overall 5-year survival was 54%; median survival was 84 months. Pretreatment FIGO stage was the single most important predictor of relapse-free and overall survival duration. For patients with Stage IA and IB tumours the 5-year actuarial relapse-free survival was 89%; for patients with stage IC and II (all substages), the 5-year relapse-free survival was 24% (P=0·001). For this latter group adjuvant single alkylating agent therapy was not adequate and alternative therapeutic regimens are required. The problem of suboptimal primary surgical staging is also addressed.

The role of adjuvant chemotherapy following primary surgery is still controversial in many forms of cancer, although there is now good evidence to suggest benefit for a proportion of patients with early-stage breast cancer and the approach can be curative in patients with osteosarcoma (Santoro & Bonadonna 1986) In patients with early (Stage I and II) ovarian cancer whose tumours have been totally resected, the benefits of adjuvant chemotherapy are less clear-cut. There have been no reported randomized studies demonstrating that postoperative treatment, either chemotherapy or radiotherapy, unequivocally improves cure rates. However, the responses seen in patients with advanced ovarian cancer have prompted the use of chemotherapy in early-stage disease. In particular, single alkylating agent therapy, until recently the most widely used form of chemotherapy for advanced disease, has gained popularity as adjuvant therapy for early-stage disease. There are few data documenting the effectiveness or otherwise of alkylating agent therapy in this setting.

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Parker *et al.* (1970) could not show any significant difference in 2-year and 5-year survival in 63 Stage I patients treated with either no postoperative therapy, single alkylating agent therapy (nitrogen mustard or chlorambucil), radiotherapy alone, or a combination of chemotherapy and radiotherapy. The adequacy of the initial surgery was the most significant predictor of long-term survival. Smith *et al.* (1975) randomized patients with early-stage or minimal residual Stage III disease to receive either abdomino-pelvic irradiation or 12 cycles of oral melphalan (0·2 mg/kg daily for 5 days every 4 weeks). The results of this trial were updated in 1980 (187 patients) and continued to show no significant survival advantage for either therapy. Hreshchyshyn *et al.* (1980) randomized 168 patients with Stage I disease to no adjuvant therapy, pelvic irradiation (50 Gy), or melphalan (0·2 mg/kg for 5 days every month for 18 months). There were no significant differences in the recurrence rates between the melphalan and control arms. Young *et al.* (1979) found no difference in relapse-free or overall survival in 56 patients with comprehensively staged IAi and IBi disease who were randomized to melphalan or observation alone. Dembo *et al.* (1979) observed that abdomino-pelvic irradiation was superior to pelvic irradiation alone or pelvic irradiation plus chlorambucil (6 mg daily for 2 years) in 116 patients with Stage IB and II disease. Five-year survival was 83% for abdomino-pelvic irradiation compared with 58% and 61% respectively for the other regimens. One criticism of this study was the low dose of chlorambucil administered. In addition, compliance may be a problem when the drug in question is administered orally.

In view of these conflicting results we have constructed a retrospective analysis of 46 patients with early (Stages I and II) ovarian cancer treated with a single alkylating agent to determine its role in an adjuvant setting.

Table 1. Details of pathology

	Tumour grade differentiation		
Histological subtype	Well	Moderate	Poor
Serous	4	3	7
Mucinous	3	1	0
Clear cell	1	7	1
Endometrioid	5	4	5
Undifferentiated	0	0	3
Mixed	0	0	2

Patients and methods

In a consecutive series of 98 patients with early-stage ovarian cancer, referred between November 1977 and July 1986, 46 treated with adjuvant alkylating therapy were studied. We have defined early ovarian cancer as International Federation of Gynaecology and Obstetrics (FIGO) Stage I or II disease in which the tumour was said to have been totally resected at primary cytoreductive surgery. The Christie Hospital is a specialist cancer referral centre, and post-surgical referrals came from several hospitals throughout the North West of England. Pre-treatment abdomino-pelvic computerized tomographic (CT) scans were also performed in 37 patients. These were reported as normal in 25 patients and as showing residual abnormalities consistent with postoperative changes in 12 patients. Patients with Stage III disease were excluded.

The remaining 52 patients were not included in the study and did not receive alkylating agent therapy for the following reasons: Stage IA, well differentiated (33) and borderline tumours (6) in whom adjuvant therapy was considered unnecessary; age>70 years (4); patient refusal (3); alternative therapies given (abdomino-pelvic irradiation (2); platinum-containing regimens (4)).

Adjuvant chemotherapy began within a median of 40 days from the date of primary surgery (31–59 interquartile range). Therapy comprised either cyclophosphamide given intravenously at a dose of 1 g/m^2 every 3 weeks for 10 cycles in 38 patients, or oral melphalan at a dose of 0·2 mg/kg daily for 5 days repeated every 6 weeks for 12 cycles in eight patients. Oral melphalan was used as a matter of policy between 1977 and 1979 whereas cyclophosphamide was used routinely after 1980.

In this analysis, efficacy of adjuvant therapy and the significance of possible prognostic factors were assessed using the end-points of relapse-free and overall survival duration. Standard tumour response categories were not applicable as no patient had assessable disease before treatment, and second-look laparotomy was not routinely performed. Relapse-free and overall survival was dated from the start of treatment to the date of tumour recurrence or death, calculated according to the method of Kaplan & Meier (1958) and compared using the log-rank test (Peto *et al.* 1976). Possible prognostic factors were examined using the models described by Cox (1972). Toxicity was defined using standard WHO grades (Miller *et al.* 1981). All histological sections were reviewed at one centre by one pathologist (C.H.B.). Histological grade was assessed as: well, moderately well or poorly differentiated (Russell 1987; Czernobilsky 1982). Follow-up was terminated for the purposes of this analysis at the end of April 1987.

We defined primary surgical staging as 'optimal' if the following criteria were satisfied: surgical procedure comprising total abdominal hysterectomy, bilateral salpingo-oophorectomy and omentectomy; peritoneal washings obtained for cytology; liver and undersurface of diaphragm thoroughly examined; and biopsies taken of suspicious para-aortic nodes or peritoneum. Informed consent was obtained in accordance with the institutional ethics committee.

Results

The study included 46 patients, 28 (61%) had Stage I tumours and 18 (39%) had Stage II disease. Further details of tumour stage, histology and grade are given in Tables 1 and 2. Details of primary surgery are shown in Table 3. For comparison we have also included the 52 patients not given adjuvant alkylating therapy. 'Optimal' surgery was performed in only 15% of patients in both groups. Total abdominal hysterectomy and bilateral salpingo-oophorectomy was done in 80% of the group given adjuvant alkylating therapy and in 72% of the group not given alkylating therapy.

With a median follow-up of 36+ months, 18 patients (37%) have relapsed, 16 of whom have subsequently died of progressive disease. One patient remains alive with recurrent disease and there has been one intercurrent death. The overall median survival was 84 months. The actuarial 2- and 5-year relapse-free survivals were 69% and 48% respectively. Overall 5-year survival was 54%. The sites of recurrent disease were pelvic mass only in three patients, abdominal and pelvic recurrence in nine, abdominal site only in five and extra-abdominal in one patient.

Cox model multivariate analysis showed that increasing FIGO stage was the single most significant adverse predictor of relapse-free (P=0·0003) and overall survival (P=0·0001). After adjusting for stage, the effects of other patient characteristics before treatment, including age, histological subtype and grade, type of chemotherapy and extent of primary surgery, were not significant. This analysis enabled a distinction to be made between patients with Stage IA and IB disease and those with more advanced stages (IC→IIC). In the former group only 2 of 19 (11%) have relapsed whereas in the latter group 16 of 27 (59%) have relapsed (Table 2). The relapse-free survival curves for these two groups are shown in Fig. 1.

Toxicity was generally mild for each form of treatment. There were no treatment-related deaths, although two patients on cyclophosphamide required intravenous antibiotics for febrile neutropenic episodes. Severe nausea and vomiting occurred in three patients, all treated with cyclophosphamide. Clinically significant haemorrhagic cystitis was not seen. To date no patient has developed secondary acute non-lymphocytic leukaemia.

For relapsed patients a variety of second-line therapy has been used including platinum-based

Table 2. Relapse rate by FIGO stage in patients selected for adjuvant alkylating therapy

FIGO stage	No. of patients (n=46)	Relapsed patients n	(%)	Actuarial relapse-free survival (%) 2 year	5 year
IAi	1	—	(0)	89	89
IAii	9	2	(22)		
IBi	4	—	(0)		
IBii	5	—	(0)		
IC	10	5	(50)	55	25
IIA	2	—	(0)		
IIB	9	6	(67)		
IIC	6	5	(83)		

Table 3. Extent of primary cytoreductive surgery

	Adjuvant alkylating therapy			
Primary surgery	Given (*n*=46)		Not given (*n*=52)	
Optimal	7 (15%)	80%	8 (15%)	73%
TAH, BSO, omentectomy only	6 (13%)		3 (6%)	
TAH, BSO only	24 (52%)		27 (52%)	
BSO only	6 (13%)	20%	6 (13%)	28%
Cystectomy only	3 (7%)		8(15%)	

TAH, Total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy.

and platinum analogue regimens. Despite this, 16 of the 18 relapsed patients have died with a median survival of only 6 months from the time of relapse.

Discussion

Most patients with ovarian cancer present with advanced (Stage III and IV) disease and the 5-year survival rate is only 10–15%. For the small group with early-stage tumours (20–30%) the prognosis is much improved. However, it is clear from surgical series that certain subgroups of patients with completely resected early-stage tumours are still at high risk of relapse; 30–40% Stage I and 60% Stage II patients can be expected to relapse within 5 years (Piver 1984). Major factors shown to influence this recurrence rate include stage, histological subtype and grade, adequacy of primary surgery, age, presence of ascites or capsular rupture and the presence of residual disease following initial surgery (Webb *et al.* 1973). In general, the significance of these prognostic factors has been analysed in patients following surgery alone. In this study we have attempted to determine the frequency of recurrence and significant prognostic factors in a group of patients treated with adjuvant alkylating agent therapy.

Our results have clearly shown that tumour stage is the most predictive factor for relapse-free and overall survival. In particular, patients with Stage IA and IB disease had significantly longer relapse-free and overall survival than patients with Stage IC and II disease. For the latter subset of patients the relapse rate of 56% (median follow-up 36+ months) is not lower than that which may be expected following surgery alone, and alkylating therapy appears inadequate. For this group, platinum-containing regimens may be more effective although there is not yet conclusive evidence for this. Our current research is directed towards defining the roles of adjuvant platinum-based chemotherapy, including intraperitoneal administration, in this high-risk group. A reassessment of the role of total abdomino-pelvic irradiation is also indicated after some promising results reported recently (Martinez *et al.* 1985; Fuller *et al.* 1987).

For patients with Stage IA and IB disease alkylating therapy may be effective (11% relapse rate) although longer follow-up is required to determine the true cure rate as late relapses can occur in women with ovarian cancer. The randomized study by Young *et al.* (1979), in which all patients had well or moderately well differentiated tumours, suggests that adjuvant therapy may not be required for this

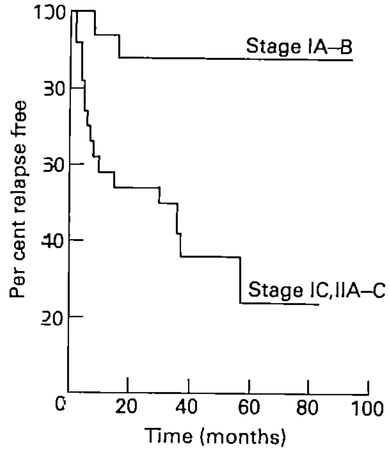

Fig. 1. Relapse-free survival according to FIGO stage. Of 19 patients with Stage IA–B disease 17 were available for follow-up at 20 months and two at 80 months. Of 27 patients with Stage IC, IIA–C disease 13 were available for follow-up at 20 months and two at 80 months P=0·001

good risk subset. Longer follow-up results from this study are awaited with interest.

It is possible that the high proportion of sub-optimal primary surgical procedures in this series may have resulted in the understaging of many patients and contributed to the high relapse rate. Although the extent of surgery was not independently predictive of relapse-free survival in our analysis, total numbers were small. The relapse rates were 29% for patients with 'optimal' surgery, 38% for those in whom hysterectomy and bilateral salpingo-oophorectomy were performed and 44% in those with lesser procedures. Surgical understaging has been frequently described in patients submitted to surgical restaging following referral to a major centre (Piver *et al.* 1978; Young *et al.* 1979); specifically, unsuspected or subclinical subdiaphragmatic metastases (5–23%), para-aortic nodes (10–15%), pelvic nodes (8–12%) and omental metastases (13–33%) have been reported. These patients will obviously have a worse prognosis than those with truly localized tumours. This is not only likely to affect the comparison of clinical trials in early-stage ovarian cancer conducted in different centres, but may also result in unsatisfactory management of patients with undetected advanced disease. Careful and comprehensive primary surgical staging is a prerequisite for defining the role of adjuvant therapy in early-stage ovarian cancer. We believe that referral correspondence after surgery should contain full details of the following procedures: total hysterectomy, bilateral salpingo-oophorectomy and omentectomy, cytological examination of peritoneal washings, biopsies of suspicious nodes or peritoneal deposits and examination of liver and undersurface of diaphragms.

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Lipoprotein and apolipoprotein levels in postmenopausal women on continuous oestrogen/progestogen therapy

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Summary. Levels of serum lipoproteins and apolipoproteins were monitored for 48 weeks in two groups of women taking part in a double-blind trial of continuous oestrogen/progestogen with and without oestriol. There were no differences between the effects of the two treatments on the substances measured. Triglycerides did not change and there was a transient fall in very low density lipoprotein cholesterol. Low density lipoprotein cholesterol fell over the first 24 weeks but rose thereafter to pretreatment levels. There was a decrease in high density lipoprotein (HDL) cholesterol due to a transient fall in HDL2 cholesterol and a gradual decrease in HDL3 cholesterol. Consequently, the only change in lipid levels present after 48 weeks was a decrease in HDL3 cholesterol, the clinical significance of which is uncertain. There was, however, an increase in apoprotein B levels and decreases in apoprotein AI and AII levels. These alterations in apoprotein levels may be unfavourable, since apoprotein B levels have been positively correlated and apoprotein AI and AII levels negatively correlated with coronary heart disease.

Postmenopausal oestrogen replacement has a beneficial effect on the lipoprotein risk factors for cardiovascular disease (Tikkanen *et al.* 1978; Hart *et al.* 1984), and several studies (Ross *et al.* 1981; Stampfer *et al.* 1985), but not all (Wilson *et al.* 1985), have suggested that the postmenopausal use of oestrogen reduces mortality from coronary heart disease. Women who have a uterus usually have a progestogen included in their postmenopausal hormone replacement therapy to prevent endometrial hyperplasia associated with oestrogen-only regimens (Whitehead *et al.* 1981). The progestogens most commonly used in combined preparations in Europe are derived from 19-nortestosterone and have androgenic as well as progestogenic action. They have adverse effects on lipoprotein profiles (Hirvonen *et al.* 1981; Farish *et al.* 1983) and may therefore negate the possible beneficial effects of oestrogen on the cardiovascular

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system. As postmenopausal hormone replacement is commonly prescribed on a long-term basis for the prevention of osteoporosis there is an increasing awareness of the need to investigate the effects of such treatment on lipoprotein metabolism.

The various lipoprotein fractions are associated differently with the risk of coronary heart disease. Several studies have shown that while low density lipoprotein (LDL) cholesterol levels are positively related, high density lipoprotein (HDL) cholesterol levels are negatively related to risk and that the HDL2 subfraction correlates better than total HDL with risk (Gordon *et al.* 1977; Miller *et al.* 1981). Plasma lipoprotein metabolism is controlled by the specific apoprotein constituents of the various lipoprotein classes and its has been suggested that apoprotein levels may be more useful than lipid levels for predicting coronary artery disease risk (Brunzell *et al.* 1984).

At present cyclical oestrogen/progestogen therapy is widely used to treat climacteric symptoms and prevent postmenopausal osteoporosis (Christiansen *et al.* 1980). However, this treatment brings with it the disadvantage of monthly bleeds and in some women dysmenorrhoea or premenstrual symptoms. To overcome these disadvantages continuous oestrogen/progestogen preparations designed to render the endometrium atrophic during the first few months of treatment are currently being assessed.

Mattsson *et al.* (1982), studying a group of women being treated with a continuous oestrogen/progestogen preparation comprising 17β-oestradiol, oestriol and norethisterone, found that climacteric symptoms were relieved and endometrial atrophy induced. However, the efficacy of oestriol in the prevention of osteoporosis and vasomotor symptoms is disputed (Lindsay *et al.* 1979). We are engaged in a study to assess the regimen without the oestriol component with reference to the treatment of vasomotor symptoms, the prevention of postmenopausal bone loss and the effects on lipoprotein profiles and to compare its effects with those of the preparation with oestriol. In this report we describe changes over 1 year in lipoprotein levels, HDL subfractions and apolipoprotein levels in postmenopausal women being treated with these preparations.

Patients and methods

Thirty-eight women attending the menopause clinics at Stobhill Hospital and the Western Infirmary, Glasgow, took part in the study. The mean age of the women was 46 years (SD 5) and they were on average 9 months from menopause. Twenty-eight had undergone hysterectomy and bilateral oophorectomy; the remainder had had a natural menopause as judged by the presence of established amenorrhoea and postmenopausal gonadotrophin levels. None of the women had received any hormone therapy in the 3 months preceding recruitment or was taking any drug liable to interfere with lipoprotein metabolism. All of the women had normal renal and hepatic function before and during treatment as indicated by routine biochemical tests, and in no case was there any contraindication to hormone replacement therapy. The study was double-blind, the two preparations being assigned randomly to the patients. Since the principal aim of the study was to assess the effects of the regimen without oestriol the preparations were randomized to groups of unequal size. They were assigned in series of six: four without and two with oestriol in random order. Twenty-six women received 2 mg oestradiol and 1 mg norethisterone acetate daily, the remaining 12 were treated with 2 mg oestradiol, 1 mg norethisterone acetate and 1 mg oestriol daily (Kliogest, Novo). Informed consent was obtained for each subject and the protocol was approved by the relevant ethics committees.

Fasting blood samples were obtained before and 12, 24 and 48 weeks after the start of treatment. Serum was separated by centrifuging at 1000 *g* for 10 min at 4°C. A portion of the serum was stored at 4°C for a maximum of 5 days before lipoprotein analysis and a further portion was stored at −20°C for apoprotein analysis. Serum triglyceride concentrations were estimated enzymatically (Bucolo & David 1973) using a Technicon RA1000. Cholesterol concentrations were estimated manually using an enzymatic technique (Allain *et al.* 1974). Very low density lipoproteins (VLDL) were separated from serum by ultracentrifugation (Airfuge, Beckman Instruments Ltd) as described previously (Farish *et al.* 1983). HDL and subfractions were quantified using the method of Eyre *et al.* (1981). LDL cholesterol levels were calculated using the formula:

LDL cholesterol = total cholesterol − (VLDL + HDL) cholesterol.

Apoprotein B levels were measured by immunodiffusion (Behringwerke, AG, Marburg). Apoprotein AI and AII levels were estimated by an immunoturbidimetric method (Rifai & King 1986) adapted for the RA1000 using commercial antisera (Boehringer Mannheim GmbH) and reference standards (Immuno Diagnostica GmbH).

The results were analysed first by a repeated measures analysis of variance to assess the effects of treatment on lipoproteins and apolipoproteins and thereafter by a repeated measures analysis of covariance using the baseline measurement as the covariate to ascertain whether there were any differences between the effects of the two regimens (Bryce 1980).

Results

Analysis of covariance revealed that there were no significant differences between the effects of the two treatments on any of the substances measured. It was therefore possible to pool the data from the two groups and only the results from the pooled data will be described in detail.

Table 1 shows the lipoprotein levels before and during treatment for each group and the combined data for the two groups. There were no statistically significant changes in triglyceride levels during treatment. Total cholesterol levels were reduced at 12 and 24 weeks but were not significantly different from baseline levels at 48 weeks. VLDL cholesterol showed a small decrease which was statistically significant at 12 weeks but the levels were not significantly different from pretreatment thereafter. LDL cholesterol levels were reduced during the first 24 weeks, but increased significantly over the following 24 weeks to pretreatment levels. There was a small decrease in HDL cholesterol levels due to a transient fall in HDL2 cholesterol at 12 weeks and a gradual fall in HDL3 cholesterol which was statistically significant at 48 weeks. The LDL:HDL cholesterol ratio did not differ significantly from baseline during treatment, nor was there any significant change in the HDL2:HDL3 cholesterol ratio.

Apoprotein B, AI and AII levels are shown in Table 2. There was a significant increase in apoprotein B during the first 12 weeks which was maintained throughout the 48 weeks. Apoprotein AI and AII levels decreased gradually and were significantly lower than baseline at 48 weeks. There were no changes in the ratios of apoproteins AI and AII to HDL cholesterol or to each other, there being a 7% decrease in all three of these analytes over the 48 weeks.

Table 1. Lipoprotein levels (mmol/l) in postmenopausal women being treated with continuous 17β-oestradiol/norethisterone (group I) or 17β-oestradiol/oestriol/norethisterone (group II)

	Group	*n*	Baseline	12 weeks	24 weeks	48 weeks
Triglyceride	I	26	1·18 (0·86)	1·10 (0·54)	1·09 (0·70)	1·18 (0·65)
	II	12	1·17 (0·36)	1·01 (0·27)	1·07 (0·34)	1·08 (0·32)
	I+II	38	1·18 (0·71)	1·07 (0·43)	1·09 (0·56)	1·14 (0·50)
Total cholesterol	I	26	5·76 (1·00)	5·28 (0·77)*	5·25 (0·75)*	5·71 (0·88)
	II	12	5·91 (0·98)	5·32 (0·95)*	5·48 (1·20)	5·66 (1·00)
	I+II	38	5·81 (1·11)	5·29 (0·83)*	5·32 (0·90)*	5·69 (0·92)
VLDL cholesterol	I	26	0·32 (0·30)	0·27 (0·17)	0·30 (0·19)	0·33 (0·26)
	II	12	0·33 (0·12)	0·24 (0·07)	0·31 (0·10)	0·26 (0·07)
	I+II	38	0·32 (0·29)	0·26 (0·14)*	0·30 (0·16)	0·31 (0·20)
LDL cholesterol	I	26	3·84 (0·89)	3·56 (0·72)	3·46 (0·70)*	3·94 (0·82)
	II	12	3·85 (0·90)	3·49 (0·92)	3·50 (1·05)	3·81 (1·10)
	I+II	38	3·84 (0·90)	3·53 (0·79)*	3·47 (0·32)*	3·89 (0·90)
HDL cholesterol	I	26	1·58 (0·29)	1·48 (0·26)	1·47 (0·27)	1·49 (0·29)
	II	12	1·75 (0·37)	1·59 (0·23)*	1·67 (0·19)	1·59 (0·27)
	I+II	38	1·63 (0·33)	1·51 (0·25)*	1·53 (0·23)*	1·52 (0·28)*
HDL2 cholesterol	I	26	0·44 (0·17)	0·39 (0·14)	0·42 (0·15)	0·43 (0·15)
	II	12	0·49 (0·17)	0·42 (0·11)	0·49 (0·09)	0·49 (0·17)
	I+II	38	0·45 (0·17)	0·40 (0·13)*	0·44 (0·13)	0·45 (0·16)
HDL3 cholesterol	I	26	1·01 (0·15)	0·98 (0·12)	0·97 (0·13)	0·96 (0·13)
	II	12	1·11 (0·20)	1·09 (0·14)	1·07 (0·15)	0·99 (0·15)
	I+II	38	1·04 (0·16)	1·02 (0·13)	1·00 (0·14)	0·97 (0·14)*

Values are means (SD).

* Significantly different from baseline $P<0{\cdot}05$.

Table 2. Apoprotein levels (g/l) in postmenopausal women being treated with continuous 17β-oestradiol/norethisterone (group I) or 17β-oestradiol/oestriol/norethisterone (group II)

	Group	*n*	Baseline	12 weeks	24 weeks	48 weeks
Apoprotein B	I	26	1·09 (0·16)	1·18 (0·20)*	1·22 (0·19)*	1·22 (0·15)*
	II	12	1·02 (0·20)	1·14 (0·22)	1·19 (0·22)*	1·12 (0·25)
	I+II	38	1·07 (0·17)	1·17 (0·21)*	1·21 (0·21)*	1·19 (0·19)*
Apoprotein AI	I	26	1·15 (0·15)	1·10 (0·14)	1·07 (0·12)	1·09 (0·15)
	II	12	1·23 (0·22)	1·15 (0·12)	1·20 (0·12)	1·11 (0·14)
	I+II	38	1·18 (0·18)	1·12 (0·13)	1·11 (0·12)	1·10 (0·15)*
Apoprotein AII	I	26	0·39 (0·06)	0·37 (0·06)	0·37 (0·06)	0·36 (0·05)
	II	12	0·40 (0·06)	0·37 (0·06)	0·37 (0·05)	0·36 (0·04)
	I+II	38	0·39 (0·06)	0·37 (0·06)	0·37 (0·06)	0·36 (0·05)*

Values are means (SD)

* Significantly different from baseline $P<0{\cdot}05$.

Apoprotein B:LDL cholesterol ratio was significantly increased throughout treatment as were the ratios of apoprotein B to apoproteins AI and AII. These ratios are shown in Table 3.

Discussion

Two previous 1-year studies of the effects on lipoproteins of similar preparations have been reported. Mattsson *et al.* (1984) studied the effects of the preparation with oestriol and found decreases in all serum lipid components with a tendency to return towards pretreatment values at 1 year although HDL cholesterol levels remained decreased. In a placebo-controlled study using the preparation without the oestriol component, Jensen *et al.* (1987) found a reduction in LDL cholesterol levels which remained significant during the year of treatment although there was an upward trend in the last 3 months. HDL levels were decreased for the first 9 months but returned to baseline levels at 1 year. However, there were significant changes in HDL in the placebo group which mirrored those of the hormone-treated group. Our findings for both treatment groups are similar to those described by Mattsson *et al.* (1984) in that we also found that downward trends in lipoprotein levels were reversed with time with the exception of HDL cholesterol levels which remained decreased during the year of treatment. The results are also similar to those found in a previous study (Fletcher *et al.* 1984) in which we monitored lipoprotein levels for 1 year in postmenopausal women being treated with a cyclical preparation comprising 17β-oestradiol and oestriol with the

Table 3. Derived ratios (g : g) in postmenopausal women being treated with 17β-oestradiol/norethisterone (group I) or 17β-oestradiol/oestriol/norethisterone (group II)

	Group	*n*	Baseline	12 weeks	24 weeks	48 weeks
Apoprotein B: LDL cholesterol	I	26	0·77 (0·09)	0·89 (0·10)*	0·94 (0·14)*	0·83 (0·11)*
	II	12	0·71 (0·11)	0·87 (0·13)*	0·93 (0·19)*	0·80 (0·17)*
	I+II	38	0·75 (0·10)	0·88 (0·11)*	0·94 (0·15)*	0·82 (0·13)*
Apoprotein B: apoprotein AI	I	26	0·96 (0·22)	1·09 (0·26)*	1·16 (0·26)*	1·16 (0·29)*
	II	12	0·88 (0·22)	0·99 (0·22)	0·96 (0·17)	1·04 (0·30)
	I+II	38	0·94 (0·22)	1·06 (0·25)*	1·09 (0·24)*	1·11 (0·29)*
Apoprotein B: apoprotein AI	I	26	2·87 (0·54)	3·24 (0·70)*	3·42 (0·77)*	3·43 (0·63)*
	II	12	2·59 (0·61)	3·15 (0·85)*	3·23 (0·57)*	3·05 (0·79)*
	I+II	38	2·78 (0·57)	3·22 (0·74)*	3·36 (0·70)*	3·31 (0·69)*

Weight ratio assuming molecular weight for cholesterol = 386.

Values are means (SD).

* Significantly different from baseline $P<0{\cdot}05$

addition of norethisterone acetate for 10 days out of 28.

Treatment with norethisterone alone has been found to cause a decrease in HDL levels within 2 months with no change thereafter and a gradual rise in LDL cholesterol which was statistically significant after 1 year of treatment (Farish *et al.* 1983). It has been reported that 17β-oestradiol causes a decrease in LDL cholesterol and an increase in HDL cholesterol within the first 2 months of treatment (Tikkanen *et al.* 1978; Fahraeus *et al.* 1982). The changes in lipoprotein levels found in the present study, therefore, reflect the effects of the individual components of the regimen. The effect of the progestogen on HDL appears to dominate that of the oestrogen, resulting in a small net decrease in this fraction. However, the decrease in the antiatherogenic HDL2 subfraction seen at 3 months was a transient one, the fall in HDL cholesterol thereafter being attributable to a reduction in the HDL3 fraction, the clinical significance of which is not known.

Although there is a considerable literature on the effects of oestrogen and progestogen replacement therapy on the lipid components of lipoproteins, little has been published on its effects on apoproteins, and to our knowledge there are no reports on the effects on apoproteins of continuous oestrogen/progestogen regimens. In the present study, apolipoprotein B, which accounts for virtually all the protein in the LDL fraction, did not change in the same manner as LDL cholesterol, but increased during the first 3 months of treatment and did not change thereafter. A similar pattern of changes was described by Ahren *et al.* (1982), who treated premenopausal women with contraceptive vaginal rings containing oestradiol and levonorgestrel and found an initial decrease in LDL cholesterol, which regained pretreatment levels by 1 year, but a steady increase in apolipoprotein B levels during the year. In a study of the effects of norethisterone acetate alone (Farish *et al.* 1986), we found an early increase in apoprotein B levels, whereas the increase in LDL cholesterol levels was only statistically significant after 1 year. Enk *et al.* (1986, 1987) studied the effects of oestradiol valerate on lipoproteins and apolipoproteins and found reductions in both LDL cholesterol and apoprotein B, although the decrease in LDL cholesterol was proportionately greater than that in apoprotein B. The findings in the present study indicate that the oestrogenic effect of this preparation is insufficient to balance the effect of norethisterone on apoprotein B. Consequently, although there was no change in LDL cholesterol after 1 year of treatment, the composition of the LDL particle had been altered to become protein enriched. This change may be associated with an increased risk for developing coronary artery disease, since several workers have reported high apoprotein B levels in normocholesterolaemic patients with atherosclerosis (Avogaro *et al.* 1979; Sniderman *et al.* 1980; Whayne *et al.* 1981).

Oestradiol and norethisterone have also been reported to affect HDL apoprotein levels. Norethisterone has been shown to decrease apoproteins AI and AII (Farish *et al.* 1986). Enk *et al.* (1987) measured apoprotein AI in patients treated with oestradiol valerate and found a significant increase, and Cheung & Albers (1977) found that women taking oestrogen therapy had higher levels of apoproteins AI and AII than those on no medication. The results of the present study indicate that the effect on HDL apoproteins of the progestogen component in this preparation is the dominant one. Reductions in levels of apoproteins AI and AII may be regarded as unfavourable, since low levels of these apoproteins have been associated with peripheral vascular disease (Bradby *et al.* 1978) and coronary artery disease (Riesen *et al.* 1980). The apoprotein B:AI and B:AII ratios were significantly increased throughout our study and these ratios are reported to be powerful discriminators for either the presence or severity of coronary artery disease (Noma *et al.* 1983). The effects on the apoproteins could perhaps be avoided by reducing the dose of norethisterone in the preparation, but the effect on the endometrium of such a reduction would have to be considered. Whitehead *et al.* (1981) found that duration of progestogen administration is more important than dose, 1 mg/day of norethisterone being as effective as 10 mg/day in suppressing endometrial stimulation by oestrogen, and they suggested that an even smaller dose may suffice.

The relation between the pharmacological alteration of lipoproteins and apoproteins, the dose, duration and type of hormone replacement, and the actual risk of developing cardiovascular disease is not yet clear. Most of the data to date (Ross *et al.* 1981; Bain *et al.* 1981; Stampfer *et al.* 1985; Henderson *et al.* 1986) suggest that the use of unopposed postmenopausal oestrogen does have a protective effect with regard to coronary heart disease. Very little is known about the long-term effects of postmenopausal replacement preparations which include progestogens (Hunt *et al.* 1987). Reports of large studies concerning the use of oral contraceptives which incorporate androgenic progestogens have pointed to an association between dosage of progestogen and occurrence of heart disease (Meade *et al.* 1980; Kay 1982), but it may be many years before sufficient data become available to assess the cardiovascular effects of postmenopausal oestrogen/progestogen therapy.

In conclusion, this study has not demonstrated that the inclusion of oestriol in this continuous preparation significantly alters its effects on lipoprotein metabolism. At the end of 1 year of treatment with either preparation the only change in the lipid moieties of the lipoproteins was a small decrease in HDL3 cholesterol, the clinical significance of which is not known, but both preparations adversely affected the apoprotein risk factors for cardiovascular disease. Whether or not the pharmacological alteration of these apoproteins changes the actual risk of developing atherosclerotic disease remains to be established.

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Peritonitis following diagnostic laparoscopy due to injury to a vesicourachal diverticulum. Case report

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Case report

A 28-year-old Chinese woman had been trying to become pregnant for the past 2 years without success. She was generally healthy and had no history of pelvic infections. She had no unusual urine or bowel symptoms. On direct questioning after the event she admitted to some intermittent umbilical discharge since childhood to which she had not attached any importance.

She was treated with clomiphene for four cycles but she did not conceive and a diagnostic laparoscopy was undertaken. The bladder was catheterized and a double puncture laparoscopy was performed under general anaesthesia. The Verres needle was inserted at the inferior border of the umbilicus. About 3 litres of carbon dioxide were insufflated and the pressure during the procedure was between 10 and 20 mmHg. A trocar and cannula replaced the Verres needle, and as a preliminary survey of the peritoneal cavity did not show any abdominal wall adhesions, a second puncture was made for the insertion of a probe in the midline just above the pubic hairline. There was no undue difficulty in any of the above steps.

The uterus was elevated with a uterine sound and the pelvic organs were inspected systematically. The pelvis appeared normal and there was a corpus luteum in the left ovary. The procedure went smoothly except for occasional cloudiness of the laparoscopic lens due to fluid dripping from above. This was easily cleared by touching the lens on the fundus of the uterus. Instillation of methylene blue dye solution through the cervix showed both tubes to be patent. There was a small amount of serous fluid in the pouch of Douglas. The pneumoperitoneum was released and the puncture wound closed. She was sent to the ward where she had a restless night during which she vomited twice. In the morning her temperature was 38°C and the lower abdomen was tense and guarded with marked rebound tenderness. The total white cell count was 5800/ml with 90% polymorphs. Her condition did not improve and a laparotomy was performed in the evening after consultation with the general surgeon.

A midline incision was made below the umbilicus and there was some difficulty in entering the peritoneum as there was some intervening tissue between the rectus sheath and the peritoneal cavity. Further dissection revealed this tissue to be a patent urachal diverticulum of the bladder extending to and ending blindly at the umbilicus (Fig. 1). At the apex of the diverticulum was a club-shaped urinary calculus measuring 3·5×1·5×1·1 cm (Fig. 2). The diverticulum, which measured 5×2×1 cm, was excised and the apex of the bladder to which it was attached was repaired in two layers. The rest of the bladder was inspected and no other diverticulum was found. There was no thickening of the bladder wall or trabeculation to suggest chronic outflow obstruction.

The whole peritoneal cavity was covered in greenish-white non-offensive pus. A fibrinous exudate was present on the surface of the bowel and the abdominal organs. The entire gastrointestinal tract was carefully inspected and found

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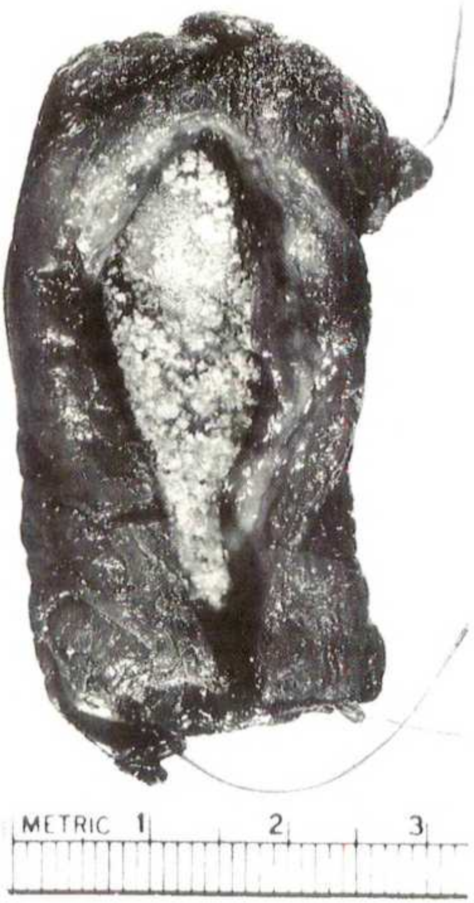

Fig. 1. Vesicourachal diverticulum containing a calculus.

to be normal. Peritoneal toilet was performed and a sample of pus was taken for culture which produced a heavy growth of *Escherichia coli* sensitive to ampicillin and gentamicin. The patient was treated with these antibiotics, and metronidazole was added from the second day to cover anaerobic organisms.

The patient made a smooth recovery. She had an indwelling urinary catheter on free drainage for 10 days postoperatively. Her residual urine was 50 ml when she left hospital 11 days after the operation. Histological examination of the excised specimen showed a diverticulum lined by transitional epithelium with prominent and extensive squamous metaplasia. Focal areas of mucosal ulceration were seen. The submucosa was oedematous with mild chronic inflammatory cellular infiltration. A muscular coat consisting of discrete bundles of smooth muscle was present. A thin inner longitudinal layer and an outer thicker circular layer were discernible. There was increased fibrosis in the wall with separation of the muscle bundles.

On review 6 months later, the abdominal wound was healed and there was no more umbilical discharge. She decided to postpone further infertility investigations.

Discussion

Urachal tract disease presenting in adulthood is exceedingly rare and in one large survey only five of 400 patients who presented with signs and symptoms were more than 20 years old (Sterling & Goldsmith 1953). The condition might not be discovered if left alone. Common presenting symptoms are recurrent umbilical discharge, urinary complications or pain if there is abscess formation. A patent omphalomesenteric duct or Meckel's diverticulum can also cause umbilical discharge (Bauer & Retik 1978).

Anatomical dissection shows considerable variation in the course of the urachus in relation to the obliterated umbilical arteries and the

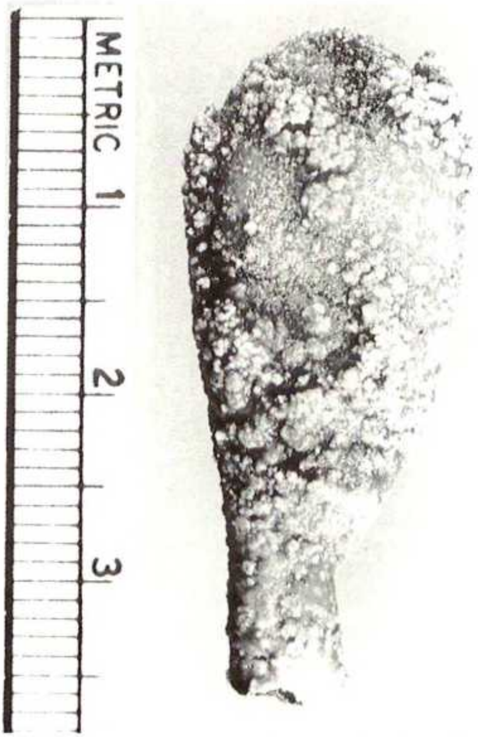

Fig. 2. The club-shaped calculus taken from the lumen of the vesicourachal diverticulum.

length of the urachus in relation to the vesicoumbilical distance (Blichert-Toft *et al.* 1973). Histological examination of the urachus usually shows a tubular structure lined by simple cuboidal or normal transitional epithelium (Blichert-Toft *et al.* 1973), abundant connective tissue and varying amount of smooth muscle (Hinman 1961).

Embryologically the urachus is part of the bladder. It is formed as the bladder descends from its early embryonic position at the umbilicus to the adult location in the pelvis. Careful dissections have revealed that the lumen of the urachus is retained throughout life and its lower end frequently communicates with the bladder near the apex (Begg 1930). Anomalies of the urachus, however, are rare. They can be in the form of congenital patent urachus, urachal cyst, umbilical urachal sinus or vesicourachal diverticulum. Of these, vesicourachal diverticulum is the most infrequent and was encountered in only 10 (3%) of 315 urachal anomalies studied (Blichert-Toft & Nielsen 1971).

Complications of urachal anomalies include urinary tract infection (Cooper & Kintzen 1962), spontaneous perforation, development of fistulous tract and abscess formation (Lazarus & Roesenthal 1945), spontaneous marsupialization of the infected urachal cyst to an abdominal viscus such as colon and ileum (Sawyer 1945), calculi formation (Snow 1957), intestinal obstruction (Haupt & Keitel 1960) and neoplastic transformation (Wilmoth 1936).

Vesicourachal diverticulum is formed as a result of failure of closure of the communication between the bladder and the urachus (Hammond *et al.* 1941). It has been postulated that bladder outlet obstruction plays an important role in the pathogenesis of vesicourachal diverticulum as a result of increased intravesical pressure on a technically patent urachus (Hinman 1961). Rarely, however, vesicourachal diverticulum of congenital origin without obstruction has been described (Trimingham & McDonald 1945; Hinman 1961). We believe our patient, being young and without evidence of bladder outlet obstruction, belongs to the latter category. Stone formation in a vesicourachal diverticulum is uncommon but not unexpected because of stasis. Calculi have also been described in urachal cysts (Snow 1957). The extensive squamous metaplasia is attributable to the chronic irritation of the concretion.

Detailed histological examination of the excised vesicourachal diverticulum revealed a blind sac lined by epithelium and with a muscular coat of varying thickness without demonstrable external communication. It was unlikely to be the source of umbilical discharge which the patient complained of. That there might be an associated umbilical urachal sinus remained a possibility. This, however, was not confirmed, as the umbilical tissue was not examined histologically.

Gynaecological laparoscopy is now used routinely for diagnostic and therapeutic investigations of infertile women. It is a relatively safe operation with a mortality rate of 2·5 to 10 per 100 000 (Chamberlain & Carron Brown 1978; Phillips *et al.* 1977). The rate of major complications, defined as those requiring laparotomy, varies from 3·7/1000 for sterilizations to 4·6/1000 for diagnostic laparoscopies (Phillips *et al.* 1977). Among the complications described are subcutaneous emphysema, extravasation of gas through the mesentery, right-sided pneumothorax, perforation of the large and small gut or bladder. Rarely, splenic, hepatic, gall-bladder and large vessel damage has been reported (Ohlgisser *et al.* 1985).

As far as we know, iatrogenic perforation to a vesicourachal diverticulum has not been reported before. It is one injury that may have serious consequences, as urine is particularly irritating to the peritoneum and is also likely to be infected, giving rise to severe peritonitis. It could be avoided only if the surgeon was aware of it.

An abdominal X-ray might have revealed the urinary calculus (Hinman 1961). A cystoscope would have confirmed the diagnosis and excision planned as an elective procedure. Voiding cystourethrograms might also be useful. A urachal cyst closed at both ends could present as an abdominal mass and this would have to be investigated before operation.

It is therefore emphasized that the presence of umbilical discharge should alert the laparoscopist to the possibility of urachal anomalies which have to be investigated before laparoscopy is performed. Although a generally safe operation in trained hands, laparoscopy does present unusual and sometimes unexpected complications, and the operation should be carried out in an institution with full facilities for laparotomy if possible or where such help is speedily available.

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CORRESPONDENCE

Genetic control of susceptibility to eclampsia and miscarriage

Dear Sir,

The data obtained by Cooper *et al.* about inheritability of eclampsia [*Br J Obstet Gynaecol* (1988) **95**, 644–653] lead them to conclude that the fetal genotype influences the susceptibility to the disease. They presumed that these genes are the human leucocyte antigen (HLA) genes or are linked to the HLA system. Their suggestion that these 'lines of investigation should be followed up further' prompted us to analyse our data regarding the HLA status of African babies born to eclamptic mothers.

The HLA status of 37 Zulu babies born to mothers with eclampsia was compared with the HLA type of 1416 blood donors of the same tribe and resident within the same hospital catchment area. The human leucocyte A and B antigens were determined by a two-stage lymphocytotoxicity test (Terasaki & McClelland 1964) on 20 ml of cord blood obtained at the time of delivery. In three stillborn babies, cord blood was insufficient and blood was taken by cardiac puncture. Only patients with all the classic features of eclampsia were included (systolic blood pressure >160 mmHg, diastolic blood pressure >115 mmHg, gross oedema and at least 2 pluses of proteinuria measured on a catheter specimen of urine by turbinometric methods). Of the 37 patients 30 had already suffered at least one seizure before admission, the other seven all had irritability or intellectual clouding and were hyper-reflexic with clonus. Mothers with previous hypertension (booking blood pressure >140/180 mmHg), a past history of renal disease and those who had not fully recovered by the seventh postpartum day to an aproteinuric normotensive state were excluded.

The B35 antigen was more prevalent in babies born to sufferers from eclampsia than one would expect (22% compared with 6·7% in the controls; relative risk 3·9, χ^2 12·2; P=0·01, using χ^2-test corrected by the Bonferoni inequality method).

This adds weight to the suggestion made by Cooper *et al.* that eclampsia may be influenced by the genetic make-up of the fetus.

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Umbilical artery flow velocity waveforms in fetuses dying with congenital anomalies

Dear Sir,

Hsieh *et al.* [*Br J Obstet Gynaecol* (1988) **95**, 478–482] suggested that zero or reversed diastolic flow in the fetal umbilical artery may be a terminal condition, on the basis of eight fetuses with anatomical abnormalities who died within a week of demonstration of this finding. We have seen a number of multiple pregnancies with zero or reversed flow in one fetus only, either very early in our assessment of Doppler studies, or too early in pregnancy to justify delivery of the healthy sibling(s). There were six pregnancies (seven fetuses), summarized below, in which fetal death or delivery was delayed at least 2 weeks; three had additional complications, and two of these were in the second trimester (we would not have undertaken Doppler studies this early in less extreme circumstances).

Case reports

(1) Fraternal twin; intrauterine growth retardation (IUGR); zero flow at 33·5 weeks; born at 35·5 weeks; birthweight 2000 g; Apgar scores 3

and 6; meconium aspiration. Initial sclerema and multi-system failure; later unilateral periventricular leuko-encephalopathy and associated neurological findings.

(2) Fraternal twin; IUGR; oligohydramnios; zero flow at 26 weeks; intraventricular haemorrhage at 29 weeks; died at 30 weeks; birthweight 230 g.

(3a) Fraternal quad; IUGR; intermittent zero flow at 27·5 weeks and for 30% of cardiac cycle at 29·5 weeks; born at 32·5 weeks; birthweight 770 g; Apgar scores 6 and 9. Neonatal course uneventful; no neurological complications.

(3b) Fraternal quad; IUGR; zero flow at 29·5 weeks; born at 32·5 weeks; birthweight 1070 g; Apgar scores 8 and 9. Uneventful neonatal course; no neurological complications.

(4) Monozygotic twin; zero flow at 33 weeks; some diastolic flow 10 days later (but less than normal); born at 35 weeks; birthweight 1380 g; Apgar scores 8 and 9. Both twins profoundly neurologically affected by fetal cytomegalovirus infection, but this twin also had evidence of an intracranial catastrophe several weeks before delivery.

(5) Monozygotic twin; recipient of twin–twin transfusion from 14·5 weeks; hydropic from 18·5 weeks; zero flow at 22 weeks; fetal death 3–4 weeks later.

(6) Fraternal twin; raised alpha-feto protein; profound IUGR; oligohydramnios and zero flow at 22 weeks; fetal death and birth at 29 weeks; birthweight 270 g; triploid.

Clearly, although zero/reversed diastolic flow is to be taken very seriously, it is not necessarily terminal. It is not known whether its impact is altered by gestational age, fetal abnormality or multiple pregnancy. One would not want to leave a fetus to tolerate it for long (particularly since it may have been present for some time before diagnosis). However, we have not found evidence to alter our original policy: that an abnormal Doppler study alone would not precipitate immediate delivery.

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Reference

Hsieh F. J., Chang F. M., Ko T M., Chen H. Y. & Chen Y. P. (1988) Umbilical artery flow velocity waveforms in fetuses dying with congenital anomalies *Br J Obstet Gynaecol* **95**, 478-482.

Serial oxytocin levels in amniotic fluid and maternal plasma during normal and induced labour

Dear Sir,

We read with interest the article by Padayachi *et al.* [*Br J Obstet Gynaecol* (1988) **95**, 888–893] reporting plasma oxytocin concentrations during human pregnancy. This is a poorly understood, yet extremely important area of clinical practice, the study of which is fraught with difficulty. One of the major problems is the degradation of oxytocin by oxytocinase, an enzyme produced by the human placenta. Padayachi *et al.* collected samples in pre-chilled EDTA tubes to prevent oxytocinase activity; phenanthrolene was omitted due to interference with the assay antibody–antigen binding. This is therefore a modification of the EDTA and phenanthrolene technique described by Burd *et al.* (1985, 1987) who emphasized that the omission of the phenanthrolene was associated with a 32% degradation of labelled oxytocin. It may therefore be unreasonable to use EDTA alone for the inhibition of oxytocinase activity.

A significant reduction in inhibitor activity occurs after 1h (even using combined inhibitors) and extraction within this time is mandatory. Do the authors have any data which indicate oxytocinase activity is completely prevented by EDTA alone with subsequent freezing of samples and extraction within 24 h?

The extraction method using Sep-Pak cartridges gives excellent recoveries of oxytocin. Nevertheless, it is essential that the process removes oxytocinase activity from the plasma to prevent degradation of radiolabelled oxytocin in the assay, leading to spuriously high results (Chard 1973). Have the authors any data on the degrading activity of the plasma extracts?

The circulating concentrations of oxytocin in human pregnancy are extremely low and a sensitive radioimmunoassay is required for research in this area. It is therefore essential to have some indication of the detection limit of the assay and the amount of exogenous oxytocin which displaces 50% of the radiolabelled oxytocin from the antibody. The sensitivity is quoted as

10 μU/ml which is greater than many of the published plasma concentrations. How does the sensitivity of the assay relate to the recorded plasma concentrations. Many authors have recorded undetectable concentrations during pregnancy. Did any of the samples from this study contain undetectable concentrations?

We would be interested in the authors' comments.

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Authors' reply

Dear Sir,

We thank Dr Thornton *et al.* for their comments and for highlighting once again the difficulties in measuring plasma oxytocin. Following the report of adequate inhibition of oxytocinase at 37°C by the use of phenanthroline (25 mg/ml) plus EDTA (1 mol/l) (Burd *et al.* 1985), we incorporated these in our sample collections. The inclusion of phenanthroline, however, consistently yielded higher oxytocin concentrations in plasma from either pregnant or non-pregnant women, males, or in buffer preparations. This effect was present at lower concentrations and was demonstrable after extraction on Seppak C18 cartridges. Samples were therefore collected in tubes containing EDTA only. In addition, the tubes were kept cold on crushed ice and the plasma separated in a refrigerated centrifuge.

In a pilot study, plasma and amniotic fluid were extracted within 1h of collection (5, 20, 40 and 60 min after withdrawal) or rapidly frozen in a solid CO_2/methanol bath and extracted 24 h later. After the extraction, the vials containing the eluate were dried in a vacuum oven and stored dried at −20°C until assay, which was usually within 1 week. The differences in the levels of oxytocin were found to be within the coefficient of variation for the assay at that concentration (approximately 10%), which suggests the absence of any marked degradation. We did not examine the activity of oxytocinase in the plasma extracts; however, when these extracts were reconstituted, their oxytocin levels were stable for a week when stored at −20°C, again suggesting the lack of any marked degradation.

The amount of oxytocin required to displace 50% of the radiolabelled ligand from the antibody was 66 μU/ml (13·2 μU/tube). Oxytocin levels were concentrated eightfold following Seppak extraction (4 ml plasma reconstituted to 500 μl), thus enabling detection of levels that are normally below the sensitivity of the assay (10 μU/ml or 2 μU/tube). None of the samples had undetectable oxytocin concentrations.

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Reference

Burd J. M., Weightman D. R. & Baylis P. H. (1985) Efficacy of inhibitors of oxytocinase activity *Clin Sci* **69**, 71P.

Classical versus low-segment transverse incision for preterm caesarean section: maternal complications and outcome of subsequent pregnancies

Dear Sir,

We were interested to read the report by Halperin *et al.* [*Br J Obstet Gynaecol* (1988) **95**, 990–996] of their experience of the delivery of preterm infants by classical caesarean section as opposed to the lower-segment transverse procedure. In a group of 326 women delivered at between 24 and 35 completed weeks gestation they observed a tendency towards a higher level of maternal postoperative morbidity and a much greater frequency of problems relating to the uterine scar in subsequent pregnancies. Despite this, they observed no differences in perinatal mortality or Apgar scores between the two modes of caesarean section.

It has been our experience (Haddad & Irvine

1988) that the neonatal outcome of the very preterm infant born by the classical (as opposed to lower-segment) route is, if anything, worse. During 1986, 17 live singletons under 30 weeks gestation were born by caesarean section in our hospital, six by the classical and 11 by the lower-segment route. Despite the fact that the groups were comparable in terms of gestation, birth-weight, and indication for delivery, only two of the six babies born by the classical route survived, compared with all of the 11 babies born by lower uterine segment caesarean section.

We would suggest that classical caesarean section for the delivery of the preterm infant should be undertaken only after full consideration has been given to the possibility of performing a lower-segment procedure.

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Authors' reply

Dear Sir,

Drs Irvine & Haddad make an important recommendation that classical caesarean section for the delivery of the preterm infant be undertaken only after full consideration has been given to the possibility of performing a lower-segment procedure.

We would agree with this because of the concern for postoperative maternal morbidity and uterine dehiscence in subsequent pregnancies. We would emphasize, however, that although the decision to make a classical incision is generally made after the abdomen is opened, the possibility that such an incision may be necessary (with its associated risks) is discussed with the patient before the caesarean section.

In our study a much larger number of babies in the classical group were in a breech or transverse lie position compared with the low-segment group (76% *vs* 32%, $P<0{\cdot}001$).

As the babies were not comparable in the two groups we did not feel we could comment on the effect of the incision on the perinatal outcome.

The perinatal outcomes, however, were similar and were as follows: 1-min Apgar score <7 (77% in the classical group; 71% in the low-segment group); 5-min Apgar score <7 (21% in the classical group; 17% in the low-segment group); perinatal mortality (17% in the classical group; 15% in the low-segment group).

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BOOK REVIEWS

Progress in Infertility. Third edition edited by S. J. Behrman, Robert W. Kistner & G. W. Patton Jr. Little, Brown & Co., Boston/Toronto, 1988, 852 pages with figures and tables, £65.00

Although of a distinctly North American flavour, *Progress in Infertility* has been one of the standard reference volumes on this side of the Atlantic since the appearance of the first edition in 1968. This is the third edition and Grant W. Patton Jr has joined the distinguished editorial duo, Behrman and Kistner. The book has moved with the times. Just as there were major changes in the second edition (1975) mainly in endocrinology and ovulation induction, so there are major additions and amendments in this edition. This is just as well as the last decade has seen fairly dramatic developments in infertility. In-vitro fertilization (IVF) has brought in its wake not only a better understanding of the pathophysiology, but also more advances and openness. This in turn has brought ethical dilemmas relating to treatment, resource allocation and embryo research.

The major change in this book is the addition of chapters on various aspects of IVF, ovarian phsyiology (the now mandatory chapter from the Hodgen group) and advances in tubal and pelvic surgery. Immunological factors have been downgraded from four chapters to one, while unexplained infertility, which was barely acknowledged as an entity in 1975, now merits a chapter of its own. Inevitably there are disappointments and omissions. In an otherwise good chapter on endometriosis, 12 pages devoted to danazol are unnecessary, while progestagen treatment is dismissed in half a page. Similarly, the absence of a chapter on the epidemiology of infertility is a weakness, particularly as the best current data in this interesting area, which has implications for health service planning, are derived from North America (US Survey of Family Growth).

In general, the chapters are comprehensive and carry extensive reference lists. Those on ovarian failure (Simpson) and laser surgery (Martin) were particularly useful additions, while in the chapter on the elusive inadequate luteal phase (Wentz) an earnest attempt was made to introduce some understanding of basic physiology. Overall, my major disappointment is that the book is stronger on treatment than on underlying mechanisms, and inevitably much of the treatment of the day will have lapsed in another decade, or at least one would hope so. While there has been an increasing tendency over the three editions to seek contributions from outside North America, disappointingly there are no British authors in this edition. Perhaps this is a reflection of the state of the art in this country, or at least the American perception. Nevertheless, this new edition will be much used and quoted, and has ensured that *Progress in Infertility* will remain one of the foremost volumes in the specialty.

A. Templeton

Sectional Fetal Anatomy in Ultrasound by Alf Staudach. Springer-Verlag, Berlin, Heidelberg, New York, 1987, 198 pages with 247 figures, DM 120

Astonishing improvements in the quality of imaging achieved by modern high-resolution diagnostic ultrasound equipment have presented the bemused ultrasonographer with much more detail of fetal anatomy, including hitherto unseen structures. Professor Staudach, as both anatomist and obstetric ultrasonographer, is ideally qualified to teach us the detailed fetal anatomy necessary for current practice. He does so masterfully in this excellent volume. Ultrasound images of first-class quality are displayed alongside anatomical sections and relevant line diagrams. The ultrasound novice may find the detail excessive but those who have mastered the basics will find this book extremely useful.

Criticisms are very minor. I did not find helpful a description of the author's experience of diagnosing fetal malformation. The English-speaking reader would find some of the illustrations easier to understand with the labels translated from German. The focus of the book is very much on normal fetal anatomy and its changing pattern with development. References to malformation are patchy and generally take the form of uninformative lists. These would seem to me better left out or, alternatively and even better, expanded by the author to make this a comprehensive text of both normal and abnormal fetal anatomy. As it stands, nonetheless, it is enthusiastically recommended to obstetric ultrasonographers of all types.

J. P. Neilson

Contemporary Issues in Fetal and Neonatal Medicine. 3. Ethical Issues at the Outset of Life edited by William B. Weil Jr & Martin Benjamin. Blackwell Scientific Publications, Oxford, 1987, 271 pages with figures and tables, £36.00

This book addresses the many ethical issues that have arisen in reproduction in recent years. The catalyst to this discussion was the birth of the first test-tube baby over 10 years ago when fertilization first occurred outside the human body.

This book is a most important contribution to the very complex ethical problems that now confront us as a result of modern reproductive technology. The moral status of the embryo and fetus are discussed and the well-known conservative and liberal arguments are rehearsed. The problems resulting from the creation of embryos are described. There is no real resolution of these as religious views will not change. Genetic screening, prenatal diagnosis and selective feticide are all mentioned and the pros and cons laid out. The ethical aspects of abortion are discussed but the rights and wrongs of this depend on deeply held convictions which cannot be changed and so the argument will continue. The new development of fetal therapy is very controversial and the conflict of refusal by the mother of treatment for her fetus comes down on the side of the mother. As long as the woman's body is invaded, placing her at some risk, her choice of in-utero therapy must be respected.

Quality of life of handicapped infants is tackled and the Baby Doe case is referred to frequently. Who can decide about quality of life as against no life at all? But someone has to and this should be a joint decision of medical attendant and parents. Different religious denominations have different viewpoints on all these problems and these are mentioned in this book.

To anyone who has been closely involved in these complex ethical issues there is nothing new in this book. The arguments are all well known. However, it does bring together all the discussion on these problems and the book will be most useful for those who have not previously studied the issues. It is certainly to be recommended on this score.

M. C. MacNaughton

Biology of Human Milk (Nestlé Nutrition Workshop Series Volume 15) edited by Lars A. Hanson. Raven Press, New York, 1988, 247 pages with figures and tables, $61.50

Those who regard breast milk simply as a source of nutrition for babies greatly underestimate this complex fluid. Recent research has added to our understanding of lactation as a biological event which not only nourishes the baby but also has anti-infective, anti-allergic, contraceptive and psychological effects. This volume, which is the most recent in the Nestlé Nutrition Workshop series, concentrates its attention on new data relating to the biology of human milk.

Under the editorship of Lars Hanson, an impressive list of contributors provide 15 chapters; the three main themes are the nutritional, endocrine and anti-infective properties of human milk. The first two chapters discuss the nutritional aspects of human milk protein and the energy content of breast milk respectively, and both refreshingly question current dogma. The importance of trace elements, vitamins, enzymes and human milk fat are discussed in separate chapters in the light of recent research findings.

It is now clear that human milk contains an astonishing array of hormones, although their physiological significance is not fully understood. One hormone which may have substantial importance is epidermal growth factor which, under experimental conditions at least, has a dramatic effect on neonatal gastrointestinal development. Future work in this area may prove to have implications for the management of preterm or growth-retarded infants.

One of the most interesting sections of the book includes those chapters dealing with the anti-infective properties of human milk, with an excellent review chapter by Lars Hanson; the antiparasitic effects of human milk are also discussed along with possible mechanisms of immunological protection.

Lactation is one biological activity which is common to all mammals so it is clear that it must have contributed to the evolutionary dominance of mammalian species. Recent research is beginning to give a clearer idea of why this is so and this volume gives us an excellent overview of important recent work. Improved understanding of the biology of human milk will put the nutritional management of the neonate on a more rational basis and this may be especially important for the increasingly large number of very low birthweight infants in our nurseries.

This book is highly recommended for all who have a special interest in infant nutrition, and Nestlé, who have taken their fair share of criticism over infant formulae, deserve credit for bringing out this excellent volume.

P. W. Howie

The Vulva edited by C. M. Ridley. Churchill Livingstone, Edinburgh, 1988, 363 pages with figures and tables, £60.00

A book as expensive as this must really be a library book—and no medical library should be without it. With its enormous bibliography and the merit of being up to date and built on the foundation of the first edition of 1975, the edifice is the definitive statement of the multiplicity of disorders which affect the vulva as skin and as an organ in its own right and in its unique climate.

For gynaecologists it is sad that the only truly gynaecological input is confined essentially to the surgery of malignancy. Today in most developed countries the establishment of combined dermatology and gynaecology clinics is becoming recognized as the best way to help the sufferers from vulval disorders, and the approach to the psychology and presentation of lesions benefits from this—greater input from gynaecologists would have rounded out the number of chapters, especially as it is psychology rather than psychiatry which is evident and the gynaecologist has experience of the patient in other ways which may be helpful in avoiding mental disease overtones. Nonetheless, under the psychiatric heading, valuable input about rape and mutilation are important, with a most chastening condition, the burning vulva syndrome, well described and essential to the understanding of the problem of these very sad patients.

Perhaps the most important chapter, particularly in the rapidly changing knowledge of the matter, is that of the epithelial tumours of the vulva—quite excellently presented and which should be read by all gynaecologists since it covers a group of disorders which are becoming more common, especially in younger women, and are of growing significance.

No other British textbook exists with this spectrum of multidisciplinary investigation and management of some of women's most distressing problems, and therefore the advice 'should be in every medical library' has more force than usual.

C. P. Douglas

The Early Days of Pregnancy (Journal of Reproduction and Fertility Supplement 36) Proceedings of a Symposium held as a Valedictory Meeting for Professor Arnold Klopper at Aberdeen, September 1987 edited by A. A. Templeton & Barbara J. Weir. Biochemical Society Book Depot, PO Box 32, Commerce Way, Colchester CO2 8HP, 1988, 217 pages with figures and tables, £28.00

Festschriften are few in our specialty, which is just as well for us book reviewers. At the best of times it is hard enough to criticize an author's efforts, but when a volume has been produced to honour a scientist who has just retired, only a brute would find fault with it and only a rival would damn it with faint praise. Nevertheless, Professor Arnold Klopper, in whose honour a conference was held in Aberdeen in 1987, is himself a model of scientific rigour and he would be mortified if the permanent record of that conference were assessed with anything short of ruthless objectivity. With *carte blanche* to carp, then, I can report that this is an excellent book. The valedictory symposium attracted a remarkably authoritative cast of speakers and chairmen, with overseas visitors from Australia, Scandinavia and America (including the Fuchses from New York), sassenachs from London, Cambridge, Leicester and Sheffield, and native Scots from Edinburgh and Aberdeen. Beginning with the endocrinology of conception cycles and ovarian function, the speakers covered embryonic signals, chromosomal abnormalities and early embryonic loss. There are chapters on the maternal reaction to implantation, endometrial proteins and prostaglandins, and placental hormones. A final clinical section discusses implantation failure and the medical interruption of early pregnancy. Though implantation failure may have a minor role in infertility, its relevance to in-vitro fertilization is fully explored. It is gratifying that most (though unfortunately not all) of the participants listed in the preface submitted manuscripts in time for the book to be produced promptly. The discussions that followed each paper are not included, but most chapters end with a paragraph of conclusions, a difficult but useful exercise at the sharp end of science. This well-edited book is a summary of the state of the art in an exciting field but will inevitably become dated. For the next few years, however, it will be a landmark in the fast-flowing tide of scientific research, and as such it is the ideal tribute to Arnold Klopper.

J. Drife

Books received some of which may be reviewed at a later date

New Reproductive Techniques. A Legal Perspective by Douglas J. Cusine. Gower Publishing Company, Aldershot, 1988, 261 pages, £25.00

Implantation: Biological and Clinical Aspects edited by Michael Chapman, Gedis Grudzinskas & Tim Chard. Springer-Verlag, London, Berlin, Heidelberg, New York, 1988, 258 pages with figures and tables, £60.00

Clinical In Vitro Fertilization Second edition edited by Carl Wood & Alan Trounson. Springer-Verlag, London, Berlin, Heidelberg, New York, 1988, 166 pages with figures and tables, £36.50

Counselling in HIV Infection and Aids edited by John Green & Alana McCreamer. Blackwell Scientific Publications, Oxford, London, 1988, 331 pages, £12.95

Obstetrical Decision Making Second edition edited by E. A. Friedman, D. B. Acker & B. P. Sachs. B. C. Decker, Inc., Toronto, Philadelphia, 1988, 320 pages with figures and tables, £38.00

Athletic Ability and the Anatomy of Motion by Rolf Wirhed. Wolfe Medical Publications Ltd, London, 1988, 133 pages fully illustrated with 337 figures, £9.95

Endocrine Management of Infertility edited by Terence J. Wilkin. Harwood Academic Publishers, Switzerland, 1988, 101 pages with figures and tables, no price given

Advances in Urology Volume 1 edited by B. Lytton, W. J. Catalana, L. I. Lippschultz & E. J. McGuire. Year Book Medical Publishers, Inc., Chicago, London, Boca Raton, 1988, 318 pages with figures and tables, £35.50

Modern Trends in Infertility and Conception Control Volume 4 edited by Edward E. Wallach & Roger D. Kempers. Year Book Medical Publishers, Inc., Chicago, London, Boca Raton, 1988, 599 pages with figures and tables, £37.50

Family Planning Handbook for Doctors Sixth edition edited by Ronald L. Kleinman. IPPF Medical Publications, London, 1988, 361 pages with figures and tables. Available from International Planned Parenthood Federation Distribution Unit, PO Box 759, Inner Circle, Regent's Park, London NW1 4LQ. $18.00 (£9.00 UK only), free of charge for those experiencing special difficulties in payment such as currency restriction

Proceedings and Symposia

Highlights on Endocrinology Proceedings of the First European Congress on Endocrinology held in Copenhagen, 1987, edited by Claus Christiansen & Bente Juel Riis. Available from Lilly Industries Ltd, Dextra Court, Chapel Hill, Basingstoke, Hampshire RG21 2SY

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COMMENTARIES

What this Journal would like to publish

The main function of this Journal over the last 95 years has been to report research. Advances in medicine are made only through properly conducted investigations, and the results must be made known and preserved for reference. Commentaries by experts on topics of current importance complement the accounts of original work and were an important innovation of the last editor. Reviews have appeared occasionally but news items have been rare. The need of obstetricians and gynaecologists for more general postgraduate education is met by many other publications and by new journals such as *Contemporary Reviews in Obstetrics and Gynaecology* and *Fetal Medicine Review*. Subscribers buy the Journal to keep up to date with developments in the speciality and to provide an archive for future reference; we shall continue to concentrate on the publication of descriptions of original work.

Research, particularly when human beings are involved, is not ethical unless properly planned and conducted. All new methods of clinical management should be investigated and proved to be effective before coming into general use. Many management policies, such as the use of routine induction of labour in prolonged pregnancy, are of uncertain value because they were not submitted to proper assessment when they were introduced. Clinical research involves the definition of objectives and the design of a study that has the power to achieve the objectives with reasonable certainty. In this issue of the Journal there are three papers which set standards and provide guidance for the planning and presentation of research. These discuss the design and reporting of observational studies (Bracken, p. 383), screening and diagnostic tests (Wald & Cuckle, p. 389) and controlled trials (Grant, p. 397). Clinical research is difficult; well-intentioned planning does not always lead to conclusive results, and defects in the design of the study may not become apparent until the data are analysed. The results of such research should often be published, as the information obtained may be the best possible in relation to a difficult clinical problem. Papers submitted to the Journal will be assessed against the checklists provided in this issue but will also be considered by an expert referee and by a statistician. Acceptance will depend on the extent to which the research has achieved its objectives (whether or not statistically significant differences were observed) and on the priority the information contained in the paper has in comparison to other papers being considered for publication.

The policy of the *British Journal of Obstetrics and Gynaecology* is to publish papers that describe work in the following categories.

(1) Prospective planned clinical research in obstetrics and gynaecology (papers dealing with andrology, contraception, neonatology, pharmacology, psychology, and urology will be accepted only if the topic has considerable clinical relevance to obstetrics and gynaecology);

(2) Observational research into the physiology of human reproduction, preference being given to studies that have relevance to clinical management;

(3) Descriptions of current clinical practice when these have audit value by setting standards or illustrating the results of management policies;

(4) Case reports that describe new and important pathology or which involve new and potentially valuable methods of diagnosis or management;

(5) Reviews of subjects of educational value to clinicians or research workers;

(6) Occasional papers of historical interest.

David B. Paintin
Editor

Pregnancies after childhood cancer

At present, with the improvements in the treatment of childhood cancer, there are an additional 600 children per annum who have survived at least 5 years from the diagnosis of their disease. A majority of these will survive into adulthood and may be considered to be cured (Hawkins 1989). These children were treated with surgery, radiotherapy and chemotherapy, all of which have both short- and long-term effects. The harmful effect of irradiating the pre-and post-pubertal gonad and producing sterility is well reported (Shalet *et al.* 1976) and this is reflected in the paucity of offspring of the survivors of childhood cancer (Byrne *et al.* 1987; Hawkins *et al.* 1988*a*). It is only recently that the numbers of these survivors have become large enough to investigate the long-term effects of their disease and its treatment on their offspring. Although these survivors were treated with what are now considered to be outdated regimens, mainly radiotherapy or surgery (Hawkins *et al.* 1988*b*), these findings are of relevance to the future as abdominal irradiation continues to be used in the treatment of some children with Wilms' tumour, neuroblastoma and rhabdomyosarcoma. The survivors, or wives of survivors, of these old regimens who become pregnant are those who are currently presenting in antenatal clinics.

Green *et al.* (1982) were the first to report an excess of low-birthweight infants (≤2500 g) to female survivors of Wilms' tumour who were abdominally irradiated in childhood, when compared to other survivors of Wilms' tumour. In addition they reported suggestive evidence of an increased perinatal mortality rate. This study was extended to a multicentre international study reported by Li *et al.* (1987) in which 30% of pregnancies in female survivors of Wilms' tumour who were irradiated ended in an adverse outcome, compared with fewer than 3% among the unirradiated female survivors and the wives of male survivors. Adverse outcome was defined in this study by the occurrence of at least one of the following: a fetal death at ≥20 weeks gestation, a neonatal death or a low-birthweight livebirth. Of the livebirths in women treated previously with abdominal irradiation for Wilms' tumour, 21% were low birthweight and the perinatal mortality rate was eight times that expected from general population rates.

In a retrospective cohort comparison of 47 Wilms' tumour survivors with 77 sibling controls (Byrne *et al.* 1988), irradiated female survivors had four times the risk of at least one of the following livebirth outcomes: preterm delivery (defined by the authors as less than 9 months gestation); low-birthweight offspring or offspring with a congenital abnormality. More female survivors than controls had a low-birthweight child (3/18 *vs* 1/36) or a child with a congenital abnormality (6/18 *vs* 3/33).

A recent British study (Hawkins & Smith 1988) reported that 45% of first-born children to women treated previously with abdominal irradiation for Wilms' tumour were low birthweight; there were insufficient numbers to comment on second and subsequent offspring. There was no evidence of a similar effect in women previously irradiated abdominally for other tumour types, but this may be due to their being treated at an older age and the uterus receiving a lower dose of radiation (Hawkins & Smith 1988). The proportion of first pregnancies ending in a miscarriage was higher in women treated previously with abdominal irradiation than in those with the same tumour type but not abdominally irradiated (9/40 *vs* 11/174, P=0·004).

There is no evidence of a similar effect among wives of male survivors in any of the four studies, nor among women who were not abdominally irradiated in the three studies with the information available (Green *et al.* 1982; Li *et al.* 1987; Hawkins & Smith 1988).

These findings strongly implicate radiotherapy as an important causative agent, although the way in which the normal physiology is affected by earlier irradiation is not obvious. Four hypotheses have been advanced as to the aetiology of these low-birthweight infants.

The first hypothesis that may explain these associations, based on animal experimentation, is that irradiation induces mutations in the germ cells of survivors and that these result in an excess of abnormal offspring (Kirk & Lyon 1982, 1984). The most comprehensive human data available relate to children born to survivors of the atomic bombs (Schull *et al.* 1981). The results of these studies are consistent with there being no clinically significant genetic effect.

The second hypothesis that may explain the association concerns reduced uterine elasticity. A lack of uterine elasticity and abdominopelvic fibrosis secondary to radiation might restrict the expansion of the uterus and result in preterm labour and low-birthweight infants (Li *et al.* 1987; Byrne *et al.* 1988). Uterine constraint would be expected to produce an increased frequency of the types of deformity seen in compressed babies, including congenital dislocation of the hip, talipes equinovarus and calcaneovalgus, skin dimples, abnormal skull shape, and Potter's syndrome (Smith 1981). However, only one study (Byrne *et al.* 1988) has found even a hint of such an association.

The third hypothesis is that congenital anomalies of the reproductive tract in female survivors of Wilms' tumour may be responsible for some of the increased frequency of adverse outcomes of pregnancy (Byrne *et al.* 1988). No adverse outcomes were observed in the 14 pregnancies in women not irradiated for Wilms' tumour, obtained by amalgamating pregnancies from Li *et al.* (1987) with those from the British study (Hawkins & Smith 1988). However, these numbers are small.

The fourth hypothesis is that the association has a vascular origin. Adequate placentation depends upon the conversion of spiral and distal radial arteries into wide bore vessels by two waves of the cytotrophoblast destroying the elastic media of these arteries (Fox 1978). These are then called uteroplacental arteries. The failure to produce uteroplacental arteries or the lack of response of uteroplacental arteries to the second wave of cytotrophoblastic invasion has been shown to be associated with low birthweight, preterm infants, small-for-gestational-age infants and the development of pre-eclampsia (Pearce 1987). Similar problems are also seen in some women who have recurrent miscarriages (Khong *et al.* 1987). One of the mechanisms for the late effects of irradiation is persistent damage to small arterioles (Casarett 1980; White 1976). This is either direct injury producing fibrinoid necrosis, sclerosis or hypoplasia of the vessels, or indirect injury secondary to strangulation of the vessels by fibrous tissue. It is reasonable to suppose that uterine arteries damaged in this way are made resistant to the two waves of cytotrophoblastic invasion and may thus cause the reduction in fetal growth that has been reported.

These findings suggest that it is prudent to regard any pregnancy in a woman irradiated abdominally in childhood, particularly if she had Wilms' tumour, as being at high risk of an adverse outcome.

Modern ultrasound and pathological techniques provide research methods for examining the hypotheses as to the aetiology of these adverse outcomes of pregnancy, particularly low-birthweight infants. Regular and careful ultrasound examinations will help to detect underlying uterine abnormalities, assess whether or not the uterus in these women is less distensible in the third trimester and monitor fetal growth. Estimates of fetal blood flow velocity waveforms in the arcuate artery and umbilical vein at 14 and 20 weeks would allow exploration of a possible vascular cause (Campbell *et al.* 1986). This could be further tested by the histological examination of the placenta, and where a caesarean section has been performed a placental site biopsy would enable a direct estimation of the maternal response to placentation as well as allowing assessment of the fibrous tissue content of the uterus.

It may be justified to store parental and offspring blood to compare their genetic compositions for evidence of possible germ cell mutation. All congenital abnormalities should be carefully recorded.

The numbers of women concerned are small and widely distributed throughout Britain. In order to investigate their pregnancies prospectively it seems appropriate to set up a register of such women and for them to be investigated according to a standard protocol, and also that all histology be examined by a pathologist with appropriate expertise. We are currently assessing the most effective method of carrying out a study to investigate the aetiology of these effects, as a prelude to co-ordinating such a study.

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Ethics and neonatal care

In the last decade the prospects for preterm babies have shown dramatic advances. But two linked events in September 1988 again exposed the moral and legal dilemmas in the care of newborn infants. The Royal College of Physicians' report, *Medical Care of the Newborn in England and Wales* (1988), highlighted unnecessary neonatal deaths because of underfunded provision of neonatal intensive care facilities. Then, the report's Secretary, consultant paediatrician Malcolm Chiswick, disclosed in a television documentary that decisions to withdraw life-saving treatment are arising more frequently.

In terms of resource consumption, the survival of preterm babies is the most significant element in the neonatal treasury. However, in some cases babies will only survive with severe mental or physical disability, or both. It is in the treatment deemed appropriate for babies born before 30 weeks gestation, where immaturity demands life-support and intensive care facilities, that the keenest ethical and legal issues are disclosed.

The emphasis placed by the Royal College of Physicians on the inadequacy and variability of intensive neonatal care provision masks important ethical dilemmas. On what principles should scarce resources be distributed? Should a baby with poor prognosis for normal development, whose parents believe in medical intervention at all costs, be given priority over one with less severe problems, whose parents regard the option of non-treatment as a blessing in disguise? At the core of the dilemma facing parents and paediatricians in neonatal units are two doubts: whether to use high-technology life-support machines to prolong the lives of infants with profound neurological or other physical abnormalities, and whether to resuscitate extremely-low-birthweight babies.

The ethical issues are hard to define, the law in the UK is unclear and public sentiment is largely untested. Legal reaction to ethical dilemmas tends to be *ad hoc* or *post facto*; two types of response can be identified. The first is illustrated by the trial and acquittal of consultant paediatrician Leonard Arthur in 1982. John Pearson, suffering from Down's syndrome and rejected by his parents, died 48 h after birth. The cause of death was originally given as bronchial pneumonia attributed to the dosage of dihydrocodeine prescribed by Arthur. When defence pathologists disclosed the presence of other congenital physical abnormalities which themselves could have been the cause of death, the original murder charge (carrying a mandatory life sentence on conviction) was replaced by a charge of attempted murder. After a generous summing up, which has since been seriously questioned, Arthur was acquitted (see Gunn & Smith 1985).

The second legal response has focused on attempts to force doctors to operate where they, either alone or with the agreement of parents, refuse to undertake life-saving operations. One such case just before Arthur's trial involved a rejected baby with Down's syndrome, Alexandra, with duodenal atresia (Re B 1981). The Court of Appeal baulked at the argument that the best interests of this particular child would be served by allowing her to die. The judges could foresee the possibility of cases of severe proven damage where the child's life was bound to be full of pain, where the prospect of life could be shown to be so demonstrably awful, where an opposite conclusion would be appropriate. In Alexandra's case, even though they regarded the parents' decision as entirely responsible, they concluded that the operation should be authorized.

More recently, two attempts have been made to challenge decisions on resource allocation made by hospital authorities in relation to young children waiting lengthy periods for heart surgery. Both attempts to obtain court orders to force surgeons to operate failed. One case involved a preterm baby with a heart defect (Walker 1987). A planned operation had been cancelled several times to allow more urgent cases to take priority. The baby was not in intensive care nor in an incubator, but monitored in a general ward. The court declined to intervene. The Health Authority had not acted unlawfully when it drew up its budget allocations, nor had it acted unreasonably to the point of irrationality. The parents' complaint was not directed to the particular operational decision, but was a general criticism of the health service. That could not be entertained by the courts. Judicial attitudes were encapsulated in the case of 4-year-old Matthew Collier, when the Court of Appeal said that they 'had no role in the general investigation of social policies and the allocation of resources' and that they 'cannot arrange hospital waiting lists' (Collier 1988). There is a tension inherent in this; the court in Alexandra's case was prepared to mandate surgery without regard to the resource implications or whether any other baby was displaced from the waiting list. In both recent cases, operations were performed soon after the court hearings.

Right-to-life proponents argue that non-treatment is an example of the consumerist attitude to life which is fostered by abortion laws and practices. But this confuses the resolution of two very different moral dilemmas. In abortion, the issue revolves around the disposal of unwanted fetuses. Non-treatment involves children who are very much wanted but whose existence will generate so much pain to themselves and possibly to their parents and siblings that their passing should be eased and secured in a responsible and responsive manner.

Very few people can be identified as holding an absolute sanctity-of-life position. Anencephalic babies cause most people to pause in their zeal for treatment for all, at any cost. Chromosomal or recessive genetic diseases, such as trisomy 18 or the very rare Lesch-Nyhan syndrome are difficult too, as is severe spina bifida. These are extremes at one end of a continuum on which the Down's syndrome baby with whom Arthur dealt is at the other. It can be argued in terms of quality-of-life prognosis that some babies on this continuum would be better off dead than alive.

Two dangers arise from the present legal lacuna, dangers which, to judge from the comments made by Malcolm Chiswick at the close of the recent documentary, we should do well to address urgently. One is that some babies with very poor prognoses are resuscitated without parents being given the option of non-treatment.

The other is that some babies are allowed to die even though their condition is not particularly serious. The first is an example of non-responsiveness, the second of non-responsibility. It should not be a matter of chance that parents and their newborn children become involved with a paediatric team led by either a heroic interventionist or a cavalier abstainer. There is a third, more suffuse result, which is that the heroic efforts to save the most marginal, vulnerable newborn babies consume resources necessarily denied those on the 'silent' and the visible waiting lists. There is an uncomfortable eugenic undertone in arguments such as this; but it is increasingly apparent that even if we cared and provided for, treated and valued, disabled people as we should, there would remain some babies for whom we are morally entitled, if not morally obliged, to consider earnestly non-treatment. These are babies for whom life would be so miserably unpleasant and limited, for whom life would not have been possible without the hospitals and technology to sustain it, that we should in the responsible use of that technology, withdraw it (Wells 1989).

In place of the legal vacuum left by *ad hoc* responses should be a set of guidelines which allow doctors and parents to make responsible and responsive decisions. An urgent task is to devise criteria which would help to identify those babies whose lives are destined to be 'so demonstrably awful' that non-treatment should be an option for the parents. The RCP Report openly eschews ethical questions but states both that all babies should be respected and treated as potentially autonomous persons and that the 'main objective' of neonatal intensive care is the maximum survival of potentially normal individuals with the minimum risk of salvaging hopelessly disabled ones. The tragic failure of our present attempts to grapple with these dilemmas is the irresolution of these two conflicting aspirations.

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Reporting observational studies

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This paper provides guidelines for reporting observational studies. Rather than providing a critique of the design and conduct of such studies the focus is on reporting their results in such a way that the research can be critically appraised. Since many papers submitted to this Journal are rejected or returned for more information because of lack of clarity in the report, the present paper should assist authors in having their studies published. The knowledge that these reporting details will be required may also help in the design of new studies.

The two major types of observational, as distinct from experimental, research design are the prospective (cohort) study and the retrospective (case-control) study. These study designs represent a very large proportion of all studies reported in the clinical and epidemiological literature. The reports of both types of study essentially follow the same format. The present paper provides 'minimal' guidelines and the careful investigator will wish to consult more detailed texts. Both types of study are described in books by Rothman (1986), Kelsey *et al.* (1986), Sackett *et al.* (1985) and Weiss (1986), the last two placing particular emphasis on clinical studies. Case-control studies have been considered by Breslow & Day (1980) and Schlesselman (1982), and cohort studies by Breslow & Day (1987). Miettinen (1985) offers detailed theoretical work underpinning observational study design and analysis. A good basic sampling text is that of Levy & Lemeshow (1980). Some particular problems in the design of perinatal case-control studies are considered by Bracken (1984). For perinatal studies in particular, procedures for determining sample size and statistical power have been described by Freeman (1984) and the multivariable analysis of case-control and cohort studies by Holford (1984). A number of study biases are mentioned in this report and a full description of them is given by Sackett (1979).

A list of 36 reasonable questions to ask in respect of reports of case-control and cohort studies is presented in Table 1. Not all of these questions are relevant to all observational studies: for example those relating to interviewer biases will clearly not be pertinent to studies conducted using clinical records. The list of questions should nevertheless be helpful as a checklist against which to assess the quality of reports of a wide range of investigations.

Introduction to the report

It is surprising how often the precise question being addressed by a study is not explicitly provided (Question 1). The literature review should be current and complete (Question 2). While an exhaustive review is not expected, if important papers known to most readers are not reviewed the study cannot be placed in its proper context. If only the author's own work is referenced, suspect ignorance, narcissism or someone so far in advance of everyone else that you will have trouble assessing their work anyway!

The overall research design should be identified clearly (Question 3). The reader should also assess whether the overall study design can properly test any specified study hypothesis (Question 4). Not infrequently, studies are designed which, however they turn out, do not test the stated hypotheses. This question should be raised again after reading the Methods section. Typically, there may be competing explanations for the study outcome which have not been, or cannot be, ruled out by the study.

Description of materials and methods

Case-control studies should include a detailed description of how both the case and control groups were assembled (Question 5). Similarly, in describing prospective studies, the precise method of defining the exposed and unexposed

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Table 1. A checklist for reports of observational studies

Introduction to the report

1. Has the specific hypothesis being addressed by the study been made explicit?
2. Is the literature review current and complete?
3. Has the research design been clearly identified?
4. Is it a design which can challenge the study hypothesis?

Description of materials and methods

5 Is there a clear exposition of how the study groups were
   (a) Initially identified or selected
   (b) Approached for entry into the study
   (c) Diagnosed or assessed
   (d) Confirmed in their diagnosis (of exposure or disease)?
6 For each stage of the study, from first identification to assessment of eligibility, interview, and entry into analysis, has the number of subjects included or excluded been tabulated?
7. If study groups were 'matched', have the rationale and detailed criteria for matching, and success (i.e. number of cases not matched) been provided?
8 If multiple control groups have been used, has the assembly of each group and its rationale been made explicit?
9. If control groups represent a population sample, have sampling fractions and full details of other sampling criteria been provided?
10. If hospital controls rather than healthy controls have been used, has the rationale been stated and reassurance given that this forms an unbiased control group?
11. If historical rather than concurrent controls have been used, has it been explained why this does not introduce bias into the study?
12. Have sample size calculations performed before the study in order to determine the required number of subjects been presented?
13 Was the study conducted in an ethical manner?
14. Were special data collection forms or existing records used, were interviewers trained in collecting data, were they aware of the study hypothesis and the status of the individuals being interviewed? What steps were taken to avoid 'interviewer bias'?
15 Was a structured data collection instrument used, was the interview conducted in a standard way, and were all interviews conducted in the same environment (home or delivery ward, for example)?
16 Has the timing of the interview with respect to the respondents' knowledge of their diagnosis, or exposure, been described?
17 Have the precise questions used in the interview in order to ascertain exposures of special interest been reported? Have measures of 'duration' and 'recency' been described?
18. Have the methods for grading the exposure to an agent, or the intensity of a treatment manoeuvre, or the stage of illness been described adequately?
19. Has the measurement of important confounding or effect-modifying variables been described so the reader can judge how they have been controlled?
20 Has reassurance been provided that the follow-up of all study groups to ascertain study outcomes has been unbiased?
21. Have all subjects been accounted for at follow-up?

Presentation of results

22 Has the basic contingency table for the study been reported (or can it be reconstructed)? Have correct measures of association been reported?
23. Do measures of association (e.g relative risks, odds ratios) have their confidence intervals reported? Are mean values accompanied by a measure of variance (standard deviation or standard error)?
24. Where data are grouped do these form natural cut-off points, or do they suggest that they have been created to 'force' an association?
25 Is the problem of 'multiple comparisons' addressed either statistically or by rational argument?
26. If the study groups were 'matched', has the appropriate analysis been done?
27 Has an analysis of potential confounding or effect modification of the principal relations been presented? Have potentially important synergistic effects been explored in the analysis?
28 Have important multivariable analyses been reported in tabular form (e.g. showing the data stratified across important variables), or as summaries of regression analyses (linear logistic or log linear models)?

Study conclusions

29. Is the conclusion based on the analysis? Are the conclusions overly liberal (e.g. stated as being 'strongly suggestive', or 'highly significant') when the data more properly suggest a chance finding? Alternatively, have important observations been ignored?
30 Have statistical associations been distinguished from causal relations? Have competing explanations for the study outcome been discussed?
31 Are there additional statistical analyses which the investigators could do to test competing explanations?
32 Is 'clinical significance' discussed in a manner which separates it from 'statistical significance'?
33 Has the power of the completed study to detect differences been reviewed?
34. Has discussion of *a priori* hypotheses been separated from discussion of *ex post facto* hypotheses?
35. Have the study results been placed in context of existing findings? Have the reasons for differences with previous work been discussed? Have fairly precise directions been given for future hypothesis testing?
36. If policy implications have been drawn from the data, have they been justified?

subjects is required. The reader should be able to assess the extent of any selection bias. The use of controls drawn from a healthy population may affect the exposure of interest as some groups (armed services and workers) are healthier than the general population. If hospital controls are used, some patients may have been overexposed to an agent, e.g. smoking, because of the illness that put them in hospital, or underexposed because of symptoms or management before hospitalization which led to avoidance of exposure. It is almost always preferable to study newly diagnosed (incident) cases when studying aetiology since the cases with an established condition may already have changed their exposure to the factors under study.

Since the loss of some subjects who are eligible for study may result in significant bias, a full accounting of all subjects, from those initially eligible to those finally analysed, should be provided (Question 6).

When a matched control group has been selected, the precise matching criteria should be given (e.g. age within 2 years, delivered at the same hospital, parity 0 or 1+). The simple statement that controls were age and parity matched is inadequate (Question 7). Similarly, if several control groups are used, the statement 'an equal number of healthy newborns were identified' would not be fully informative. The reader should be told why the control group is important (which biases it protects against), and how subjects were selected (Question 8). It is advantageous if control groups can be selected from a known population (e.g. a random sample of all healthy newborns) since a number of useful statistics, including incidence, exposure prevalence, and attributable risks (Walter 1978) can be calculated. If sampling is used, the procedures (e.g. simple, cluster or stratified sampling) and the sampling fractions should be described (Question 9).

In some studies the control group may be other patients in the same hospital. For example, if studying the aetiology of a congenital malformation, mothers of children with another type of malformation are sometimes selected as controls for reasons of convenience and to protect against possible recall bias. The use of 'diseased' rather than healthy controls is fraught with potential problems and requires justification and a description of how this may affect the results of the study (Question 10). Historical comparison groups developed from past patients are also problematic, and the rationale and implications of using them should be presented (Question 11).

In a well-planned study the investigators will have calculated, in advance of data collection: first, the size of the difference in disease rates (prospective studies) or exposure (case-control studies) which are of clinical or public health importance and which the study is capable of detecting at a specified increased level of risk; second, the probability which the investigators are willing to accept for reporting a real study difference when, in fact, no difference exists (typically 5% and called Type I error); and third, the probability of failing to identify real study differences (typically set at 10 or 20% and called Type II error). From these three estimations the investigators should have calculated the number of patients required for their study (Question 12).

The Journal has a clear interest in assuring that the research it publishes has been performed in an ethical manner and the report should affirm that all participants in prospective studies were fully informed about what their involvement in the study required and that participation was voluntary (Question 13).

Bias in a study may arise during data collection. The reader should be told whether the data were collected from existing medical records or from specifically designed data collection instruments. If interviewers were used, were they aware of the study hypothesis, the status of the individuals being interviewed, and did they all have an equal chance of interviewing exposed and unexposed subjects, or cases and controls (Question 14)? Was a structured or open-ended interview used and was the interview conducted using a standard format? For example, were introductory remarks standardized and were respondent's questions postponed, as far as possible, until the end of the interview? Where did the interview take place (home or hospital) and was it the same for all subjects (Question 15)?

Readers should be informed of other factors which may bias data collection. If subjects with a disease have been alerted to the possible risks of some exposures because of recent publicity, or if exposed people are more aware of the need to be screened (and diagnosed) serious bias may occur (Question 16).

The precise method of obtaining information about the major variables of interest should be described (Question 17). If the study is of oral contraception, for example, the reader should be told precisely how information about oral contraceptives was obtained, the time intervals studied, the questions asked, whether women were shown 'pill books' to remind them of the available brands, how oestrogen and progestogen components were identified, how steroid doses were grouped, how women who had only used oral contraception for one incomplete cycle were classified, and so on. Many studies use measures of 'duration' and 'recency' of exposure to an agent and these should be described.

The causal interpretation of a statistical association is always enhanced when a 'dose response' is identified (Question 18). In its simplest form this will be a linear relation. If maternal caffeine use causes low birthweight, for example, then greater caffeine intake should be related to a higher risk of low birthweight than moderate caffeine use which, in turn, is related to a greater risk than no use. The development of graded scales for exposure and disease needs careful explanation. It is always preferable to have one of the exposure levels as being truly unexposed rather than low exposure (e.g. 'no' rather than 'low' caffeine use).

The measurement of potential confounding or effect-modifying variables should be described, especially if they are important modifiers of the reported association (Question 19). For example, if caffeine is found to be associated with low birthweight and caffeine users also smoke more than non-users, the reader will need to be reassured that all the residual effects of smoking have been controlled. Simply classifying subjects as smokers and non-smokers would be inadequate and a more detailed stratification required.

The intensity with which follow-up information is sought and obtained can greatly influence the study results. The reader should be informed about follow-up procedures so that an assessment about possible bias can be made. Ideally, exposed and unexposed subjects, and cases and controls, are followed up with equal rigour. If a more intensive search were made for congenital malformations in the offspring of women known to be exposed to a drug than in those of unexposed women, an erroneous result implying teratogenicity would be likely (Question 20). If any subjects cannot be followed up they must be accounted for and reasons for not following them must be provided. In studies with mortality as an end-point, failure to account for all patients could bias effect estimates since deceased patients may be disproportionately lost to follow-up (Question 21).

Presentation of results

Most observational studies result in a basic contingency table. For prospective studies with a simple dichotomy for exposure and disease this table is as follows:

	Disease	No disease
Exposed	a	b
Unexposed	c	d

Where exposure represents the primary treatment, management, behaviour or drug of interest, and disease is the major outcome. In some studies there may be several gradations of exposure or disease or both. In all studies this table should either be explicitly reported or easily reconstructed from the data presented (Question 22). The appropriate estimate of the effect of exposure from this table is the relative risk (RR) (or risk ratio) where

$$\mathrm{RR} = \frac{a}{a+b} \div \frac{c}{c+d}$$

The estimate is reported with a confidence interval, usually 95% CI. Effect estimation, rather than a simple reliance on P values, to report study results is preferable. Gardner & Altman (1986) provide a useful discussion of this point. Prospective and retrospective studies may also have continuous outcomes (e.g. birthweight or blood pressure). For these a comparison of mean values should be accompanied by their standard deviations or standard errors (Question 23).

For case-control studies the effect estimate takes a different form. Using the above table:

$$\text{Odds ratio} = \frac{a}{a+c} \div \frac{b}{b+d}$$

when the exposure rates are low (usually <10%) this simplifies to ad/bc.

When data have been grouped it is important to note whether this itself may have spuriously produced an association (Question 24). An unexposed (rather than low exposed) group is preferable if the data permit (Question 18) and other categories should form natural groups, e.g. cigarette use as 0, 1–10, 11–20, 21+ or natural statistical groups such as tertiles, or quartiles.

When many associations are studied there is an increased likelihood of Type I error. For example, in screening 20 possible drugs for their association with 30 birth defects we would expect 30 associations to be statistically significant (nominal $P<0{\cdot}05$) by chance alone among the 600 associations studied. Whether or not one corrects statistically for the effect of multiple comparisons is debatable (Bracken 1984). Many readers would like to see important associations reported both with and without such a correction. At the very least there should be some discussion about the effect of multiple comparisons on the observed results (Question 25).

If the case and control groups were matched (Question 7) they may be 'frequency matched' within fairly broad categories (say, 10-year age groups or by hospital where treated) or 'individually matched' when a control subject is picked specifically to match a case, usually on fairly narrow criteria (e.g. age within a year, sex, next baby delivered). Frequency matching is performed to reduce variability in the comparison groups and individual matching to avoid bias from an important confounding variable. The analysis of matched studies should use an appropriate analysis for matched pairs (Question 26). If there are two, three or more individually matched controls for each case then an analysis appropriate for this design should be performed. Failure to use a matched analysis for a matched study will, in general, lead to underestimation of relations in the data (Schlesselman 1982).

One of the more common omissions in reporting observational studies is a full accounting of the analysis for potential confounding variables (Question 27). It has been common practice to consider a variable as confounding only if it is associated both with the exposure variable and with the disease of interest at some nominal level of significance (usually $P<0{\cdot}05$) Because this approach may miss synergistic effects, for example, a drug may only cause birth defects if taken in combination with a second drug, a more liberal approach to identifying confounders and entering them into multivariable models is recommended (Bracken 1984). Often prescreening for potential confounding variables uses a higher P value (say $P<0{\cdot}2$) and some variables may be modelled because of their importance in the literature even if they are not significant in the data set being studied. For example, most readers would like to see cigarette smoking in a multivariable analysis of birthweight even if it did not relate significantly to birthweight in a particular study.

Important confounding variables may be analysed by matching (Question 26) or by stratification (reporting the exposure–disease relation within levels of the confounding variable), an approach usually reserved for important effect modifiers. Alternatively, multivariable analyses are reported as the 'final model' of a series of multiple regression analyses (Question 28). The most powerful multivariable analyses use either linear logistic regression (if the independent variables are a mix of continuous and categorical variables) or log linear modelling if all the variables are categorical (Holford 1984).

Study conclusions

It is important that conclusions drawn from a study are not overstated (Question 29). In an observational study a relation which has been observed and which cannot be explained by chance (Question 23), or other confounding variables (Question 27), should still be reported cautiously. The study may be the 1 in 20 expected by chance to experience Type I error (Question 12). This is particularly true if it is the first study to report the relation. Other investigators may have studied the same relation but, because of negative results, decided not to publish—a bias known as 'positive results bias' (Sackett 1979)! Studies where the observed relations may be due to chance should be clearly reported as such. Investigators (and journal editors) sometimes underestimate the importance of reliable 'negative' studies which, in fact, provide very positive information. In focusing on the major study findings, important ancillary observations must not be ignored (Question 29).

Relations observed in case-control studies should never be reported as being 'causal' since one of the key requirements of determining a causal relation, that exposure to the agent should precede the disease, can never be confirmed by a retrospective study (Question 30). Even in prospective observational studies few investigators will be bold enough to represent their findings as demonstrating causality. In observational research the declaration of a relation as being causal is offered only when several studies report the same finding, there is a reasonable biological explanation, and all other known confounding variables have been accounted for.

Discussion of observational studies should include a review of competing explanations for the observed relation. If these can be addressed by the study's own data, then a report of the analyses should be provided (Question 31). Discussion of the study results may be confused by using the term 'significant' in terms of the clinical importance of a relation and also the statistical use of the term (Question 32). Some statistically significant relations may have relatively minor clinical or public health importance because the exposure being studied is so rare.

If the study failed to include its planned number of subjects, or if the actual prevalence of exposure to an agent being studied was less than anticipated, the reader will need to be provided with a recalculation of the study's power (Question 12) so that the power of the completed study can be judged (Question 33). This is particularly important when a statistically non-significant relation is being reported since the study may simply have inadequate power to detect a clinically important association.

Observations which are data dependent, i.e. were not hypothesized before the study began, should be differentiated from *a priori* hypotheses which the study was designed to test (Question 34). In many large perinatal studies the great majority of hypotheses tested are *ex post facto,* which does not necessarily invalidate the observation, but they should be identified as such.

The results of the study should be placed within the context of existing knowledge (Question 35). If the study conflicts with other reports then it behoves the investigator to discuss the possible reasons for discrepancy, particularly with respect to differences in the populations studied, and in the way exposure, disease, and confounding variables were assessed in the conflicting studies.

All good research leads to new investigations to clarify or specify a particular relation further. The investigator should provide direction for future research in fairly specific terms (Question 35). Because many issues in perinatal research are the focus of attention by legislators, lawyers, policy makers and the public, many investigators find their research invested with more credibility than they themselves feel it merits. A careful discussion of the policy implications, or lack of them, of a particular finding is increasingly necessary (Question 36).

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Reporting the assessment of screening and diagnostic tests

NICHOLAS WALD, HOWARD CUCKLE

This paper is intended to assist those reporting the results of screening and diagnostic tests. It aims to provide guidance on what information is needed and how it can be presented so that readers may make a fair assessment of the performance of the test. First the principles and concepts underlying the evaluation of the performance of tests are outlined. From this a checklist is derived containing 29 questions which authors might like to bear in mind when composing their reports. We have numbered the questions in our checklist and refer to them in our text as they arise. To preserve the flow of the text and the structure of the checklist, the question numbers in the text are not in exactly the same sequence as they are in the checklist. We recognize that no general checklist can deal adequately with the particular and that, if adopted uncritically, a checklist can artificially constrain the presentation of data and hence the conclusions that can be drawn from them. Notwithstanding these drawbacks, we offer the checklist in the hope that it will be interpreted flexibly and may prove to be helpful. In preparing this paper, we have drawn from *Antenatal and Neonatal Screening* (Wald 1984) and in particular from the chapter on 'Principles of Screening' by Cuckle & Wald (1984).

The distinction between screening and diagnostic tests is mainly one of purpose (Question 1). Screening has been defined as the identification, among apparently healthy individuals, of those who are sufficiently at risk of a specific disorder to justify a subsequent diagnostic test or procedure, or in certain circumstances, direct preventive action. It differs from a diagnostic test in that there is no intention to make a diagnosis or to offer therapeutic intervention solely on the basis of a positive screening result.

Screening tests

Screening represents a radical departure from traditional medicine for it is usually concerned with the detection of disorders at an asymptomatic stage which cannot, therefore, have prompted the patient to seek medical attention; indeed if often involves seeking out such asymptomatic individuals among people who are not receiving any type of medical attention. It is tempting to believe that the early detection of disease is a good thing and an end in itself, forgetting that the identification of either trivial or untreatable conditions may cause anxiety with no benefit. Screening must, therefore, be principally concerned with the prevention of disease and the recognition that it is only worthwhile screening for disorders which lend themselves to effective intervention.

A screening test which separates a group at high risk from the general population may involve no more than a simple enquiry such as asking a woman her age when screening for Down's syndrome or asking whether an individual has an affected close relative when identifying carriers of certain genetic disorders. Such screening tests are so simple as often to escape recognition as tests.

Screening seeks to identify subjects who are at high risk of a specific disorder. The disorder should be well defined (Question 4) and distinct from the screening test (Question 5). The tendency to regard having a positive screening result as a disorder in itself should be avoided. For example measuring a person's blood pressure should not be regarded as a screening procedure for hypertension. The circularity confuses the

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issue and makes the assessment of screening impossible. Sometimes the distinction between test and disorder is difficult to make because a positive screening test result will, on ethical grounds, always lead to treatment before the disorder occurs. The measurement of plasma thyroxine or thyroid stimulating hormone in newborn infants as screening tests for cretinism provides an extreme example. A positive result will usually lead to treatment to prevent the development of cretinism. In such circumstances, distinguishing the test from the disorder is impossible, but awareness of the problem can avoid obvious errors in the assessment of screening, for example by a trial of the withdrawal of treatment in later life to identify possible false positives.

Assessing those who are at sufficiently high risk of a specific disorder to justify further action involves striking a balance, in the population concerned, between the severity of the disorder, its natural history (Questions 6 and 7) and its prevalence (Questions 8 and 9) on the one hand, and the availability, acceptability and hazards of diagnosis and treatment (Questions 10–12) on the other.

Screening tests, unlike tests in clinical practice, are applied to apparently healthy individuals and this raises special ethical considerations. In clinical practice the physician's obligation is to treat the patient in the best way possible, even if there is incomplete knowledge about the disease or its remedy. In screening there is an obligation not to initiate any action unless the full consequences of doing so are known and there is an effective remedy available.

Assessing a screening test

To assess the performance of a screening test, two facts need to be established. (1) The extent to which the test can discriminate affected from unaffected individuals (Questions 13–15) (2) The odds of being affected among those who have positive screening results.

The first is determined by estimating the detection rate and the false-positive rate of the screening test. The second is determined by estimating the odds of being affected given a positive result.

The *detection rate* (DR) is the percentage of affected individuals yielding a positive result (Question 16). For example, if there were 100 affected individuals and 80 of them were positive, the detection rate would be 80%. The DR of a test is also known as the sensitivity of the test.

The *false-positive rate* (FPR) is the percentage of unaffected individuals yielding a positive result (Question 18). For example if there were 100 unaffected individuals and three of them were positive the false-positive rate would be 3%. The FPR of a test can also be given by the specificity of the test using the relationship: specificity=100%−FPR. [It should be noted that some people use this term differently to describe the proportion of all test positives which are false-positive (1−positive predictive value; see below); this is not the meaning used here].

For quantitative screening tests, the DR and FPR relate to a specific cut-off level which distinguishes positive from negative results (Question 20). It is important to note that there is usually no natural cut-off level that should be adopted automatically for a particular screening test since there is usually overlap between the distribution of values for affected and unaffected individuals; moving the cut-off level to reduce the FPR will automatically reduce the DR. Only if the overlap between the distributions is negligible will the cut-off level be obvious. For some qualitative tests there may be more than one possible definition of a positive result and corresponding DR and FPR (Question 15) (e.g. CIN I would not be regarded as positive in some screening programmes for cervical cancer).

The DR is usually estimated using data relating to a complete series of individuals with the disorder, taking care not to overlook any with negative results (Question 17). Similarly the FPR is estimated from a series of unaffected individuals, although for rare disorders it is not as important to ensure the exclusion of every affected individual. Sometimes it is not possible to determine the DR and FPR directly because therapeutic intervention is usually administered before the disorder being screened for becomes manifest. In such circumstances, indirect estimates may be possible. For example in screening for cervical cancer in pregnancy, when finding a positive smear is relatively common while invasive disease over the next decade is very rare, the overall positive rate (including both true and false positives) will be a reasonable estimate of the false-positive rate. Estimating the DR is, however, more difficult; if the intervention is effective, then overt disease which would otherwise occur will be prevented, suggesting a falsely low DR. Unfortunately, there is no completely satisfactory solution. One approach is to compare the prevalence of the disease in an unscreened population with that in a population which was screened and found to have negative results. This does not, of course, exclude the possibility that the two groups may, to some extent, have had a different prevalence even in the absence of screening. This can only be completely overcome by a randomized clinical trial of screening.

The *odds of being affected given a positive result* (OAPR) is the ratio of the number of true positives to the number of false positives (Questions 19 and 20). For example, if there were 100 positives, of whom 80 were affected and 20 were not, the OAPR would be 80:20 or 4:1.

OAPR expressed as a probability is known as the positive predictive value (PPV). The PPV in our example is 80/100 or 80%. There are reasons for preferring the use of OAPR to the use of PPV. OAPRs are numerically easier to compute when a series of screening tests are performed in sequence (see below) and they provide a better impression of the relative performance of tests. For example, a test that is associated with 90 affected subjects out of 100 positives would yield an OAPR of 90:10 or 9:1, about twice as good as the OAPR of 4:1 in our example above. But the equivalent PPVs are 90% and 80%, respectively, which conceals the size of the improvement in performance.

Unlike the DR and FPR the OAPR depends on the prevalence of the disorder being screened for (Question 8). It is therefore not a property of the test itself but rather of its application. The prevalence is not always simple to determine (Question 9). It will usually be necessary to refer to reports of community-based epidemiological surveys. An estimate of the prevalence from hospital data may be misleading.

Thus the performance of a test is determined by three parameters only, two concerned with the test itself, the DR and FPR, and one with the disorder, the prevalence. Before a test is applied in practice, reasonable estimates of all three parameters should be available.

A convenient way to illustrate the performance of a screening test is to construct a flow diagram, starting with, say, 100 000 individuals being screened (Question 21). The first step is to divide these 100 000 individuals into those who are affected and those who are unaffected. Figure 1 illustrates such a flow chart for a disorder with a prevalence of 2:1000 and a screening test with a DR of 80% and a FPR of 3%. In the example the OAPR is 160:2994 or 1:19 (a PPV of 5%). The prevalence of the disorder has a marked effect on the performance of screening; if the prevalence of the disorder were 1:1000 the OAPR would be reduced to 1:37 with no change in the DR or FPR (Fig. 2).

Sometimes a screening test is one of several tests (Question 2). A flow diagram will help to illustrate the effect of introducing a second screening test performed on individuals whose first test is positive (Question 3) (Fig. 3). Ideally, the DR and FPR of the second test should be directly determined on individuals whose first test was positive. However, this is not always possible because of the scarcity of the appropriate data. In such circumstances it should not be assumed that the DR and FPR are similar to the rates for the general population without first collecting sufficient data to exclude the possibility of a substantial correlation between individual test values for the two tests among both affected and unaffected subjects. If substantial correlation were found, this would need to be allowed for and appropriate estimates of DR and FPR made. Similar considerations apply when a test is performed only on individuals whose first test is negative, as can sometimes occur; for example, an 'anomaly' ultrasound scan designed to diagnose spina bifida that may be performed routinely at, say, 20 weeks gestation when the maternal serum alpha-fetoprotein (AFP) screening test for the same disorder is done at 16–18 weeks gestation. To estmate the effects of such a policy it would be necessary to know the DR and FPR of ultrasound in women with negative serum AFP screening tests.

When a second screening test is performed on *all* individuals, not just those with positive screening results in the first test, the most efficient way of combining the information is to estimate each individual's risk of the disorder (see below) and use the risk as the screening variable itself (Question 3). This has been proposed as a method of screening for Down's syndrome, using maternal age, serum AFP, unconjugated oestriol and human chorionic gonadotrophin together.

The decision on what cut-off level to adopt can be facilitated by deriving frequency distribution curves for affected and unaffected individuals.

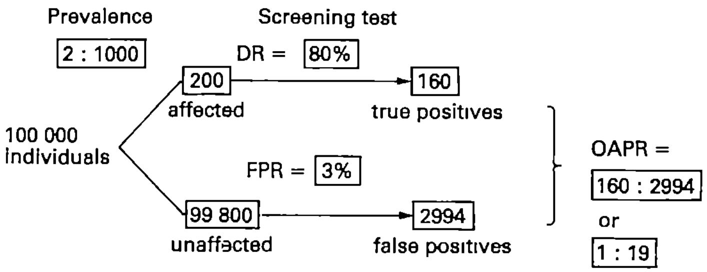

Fig. 1. Example of a flow diagram illustrating the effects of screening for a disorder with a prevalence of 2:1000 The screening test has a detection rate (DR) of 80% and a false-positive rate (FPR) of 3% OAPR=odds of being affected given a positive result

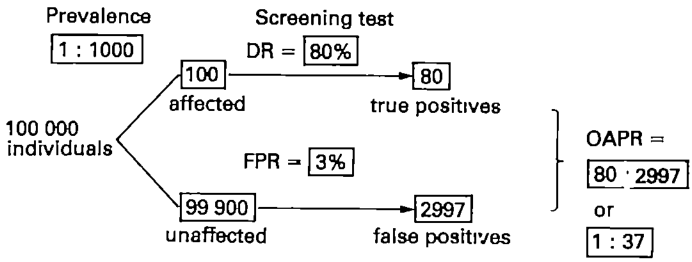

Fig. 2. Performance of the same test used in Fig. 1 but using a population in which the prevalence of the disorder is 1:1000 instead of 2:1000. OAPR=odds of being affected given a positive result.

These curves are constructed in such a way that the area under the curve to the right of a given value of the screening variable represents the percentage of individuals having that value or greater. Figures 4 and 5 show such curves and arbitrary cut-off levels at 6 and 7 units of the screening variable. The DR is given by the area under the affected curve to the right of the respective cut-off level; the FPR is given by the area under the unaffected curve to the right of the same cut-off level. The factor DR/FPR is the likelihood ratio (LR). This is the factor by which the prevalence (expressed as an odds) is multiplied to yield the OAPR. The use of the likelihood ratio in this way permits the calculation of OAPR without constructing a flow diagram.

The OAPR represents the average chance of being affected for all individuals with positive results. For a particular individual with a given positive result, the chance of being affected is

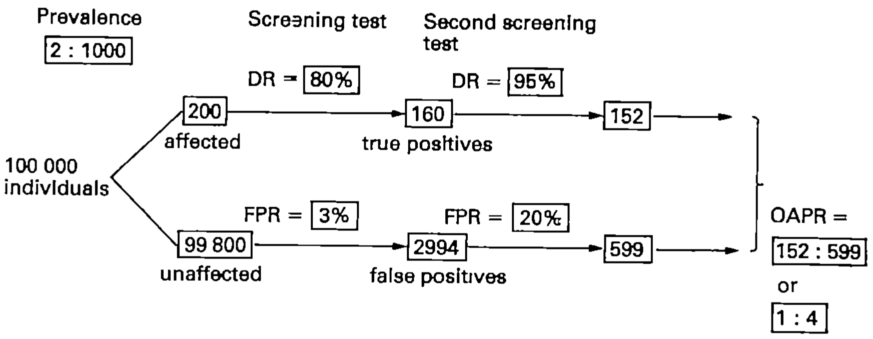

Fig. 3. Flow diagram as in Fig. 1 with the addition of a second screening test performed on individuals with positive first tests. The test has a detection rate (DR) of 95% and a false-positive rate (FPR) of 20%. OAPR=odds of being affected given a positive result.

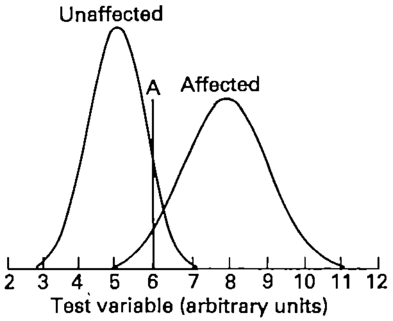

Fig. 4. Relative frequency distribution of a test variable in affected and unaffected individuals: the effect of using cut-off level 'A'. Calculation of the OAPR if the prevalence of the disorder is 2:1000

LR=DR/FPR=95%/10%=9·5
OAPR=LR×background prevalence
=9·5×2:1000
=19:1000 (or PPV=2%).

Abbreviations: DR, Detection rate; FPR; false-positive rate; LR, likelihood ratio; OAPR, odds of being affected given a positive result; PPV, positive predictive value.

calculated from the likelihood ratio defined not by the DR and FPR but by the ratio of the heights of the two frequency distribution curves at that point. While those responsible for planning screening programmes are mainly interested in the OAPR, those responsible for counselling individuals need to know the risk of being affected for the particular individual.

When assessing screening tests for chronic diseases there are a number of special problems. First, obtaining estimates of DR and FPR is difficult, both because missed cases may surface only many years later and because in some instances a positive screening test can lead directly to therapeutic action such as in screening for cancer of the cervix. Second, it may not be possible to assess the treatment separately from the assessment of the performance of the screening test because it would be unethical to leave a screen-positive individual untreated. This means that the assessment of screening is in effect a combined assessment of the effect of screening and treatment, without being able to apportion the benefits between the two.

An unacceptable method in assessment of screening for chronic diseases is to determine whether it increases survival in screen-positive individuals compared with cases that present clinically. This comparison of the survival times is subject to two biases namely, 'lead time' and 'length' bias. The lead time bias arises from the fact that even if a particular treatment were completely ineffective, the time from diagnosis to death would be longer in the cases detected by screening than in those detected clinically, simply because the cases identified by screening were detected at an earlier stage in their natural history. The length bias arises from variation between individuals in the natural history of their disease. Those with rapidly progressive disease will have only a short subclinical stage and may present clinically before there is a possibility of screening, whereas with cases exhibiting a slower course there is more time for them to be found by screening during the subclinical stage. Therefore, regardless of the efficacy of treatment, screen-positive cases will appear to live longer than those that are detected clinically.

The only reliable way of avoiding these two biases is to use age-specific mortality rate from the disease in question (not mortality for all causes combined, which is an insensitive test of screening efficacy) as the end-point since this does not depend upon survival time. A further bias due to individuals who accept screening being, in any case, at a lower or higher risk of dying from the disease can only be avoided with certainty by conducting a randomized trial of screening. The efficacy can then simply be judged by the difference in the age-specific mortality between the group randomized to the screened group and the unscreened control group.

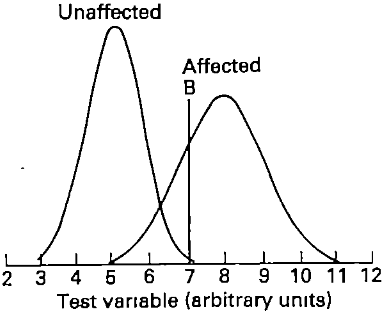

Fig. 5. Relative frequency distribution as in Fig. 4 but using a higher cut-off level 'B'.

LR=DR/FPR=80%/0·5%=160
OAPR=LR×background prevalence
=160×2:1000
=320:1000 (or PPV=24%).

Abbreviations: See Fig. 4.

The costs and benefits of screening can be considered both in financial and medical terms (Questions 22–24). The *financial* costs and benefits can be estimated by first calculating the cost of screening, say, 1000 individuals and the number of cases detected per 1000 screenees, so yielding the cost per case detected. Then the financial outlay associated with the care and treatment that is avoided by early detection can be calculated on the basis of expenditure per case detected. Estimated savings and costs per case detected then provide a simple summary of the financial cost–benefit ratio. For most screening programmes the total cost will be influenced mainly by the cost of the initial screening test so that, for screening to be cost effective, the test must be simple and economical. Estimating the *medical* costs and benefits is not straightforward because it usually involves the comparison of incommensurable outcomes. More complex economic appraisals can be performed but are usually unnecessary and are liable to obscure the main costs and benefits. For example, how many miscarriages induced by amniocentesis are acceptable in relation to preventing the birth of one handicapped child? It is inappropriate to assume automatically that one fetus lost through the trauma of amniocentesis is equal to, say, the identification and termination of one pregnancy associated with Down's syndrome.

Diagnostic tests

A diagnostic test is a test performed to make a diagnosis. This does not mean that the test is without error; there are probably no perfect tests in medicine. The term merely implies that an individual with a positive result will be offered therapeutic intervention.

The assessment of diagnostic tests, like the assessment of screening tests, involves the determination of the DR, FPR and OAPR, in the same way as with screening tests In general, diagnostic tests, to be acceptable, will be performed on only a small proportion of the population known to be at increased risk of the disorder. Diagnostic tests need to have a DR that is much higher than would be acceptable for screening tests. For example, a screening test with a DR of 60% would be acceptable, but a diagnostic test with a DR less than about 95% would not be acceptable. Because diagnostic tests are used generally only on a restricted basis among high-risk individuals, they can be acceptable in spite of being associated with some degree of hazard. Otherwise the assessment of diagnostic tests is not different from the assessment of screening tests. The fact that this section on diagnostic tests is shorter than the previous one on screening tests is simply to avoid repetition; its shorter length should not be taken to mean that the assessment of a diagnostic test is any less important than the assessment of a screening test.

Diagnostic tests can be performed as the final (or near final) step in a screening process or, more usually in ordinary clinical practice, on individuals with symptoms who seek medical help. In so far as they are used in a screening programme, they should be adopted only if the whole programme is, in the light of the questions listed in Table 1, judged to be worthwhile. The remarks made above regarding the estimation of DR and FPR for second screening tests also apply to diagnostic tests used in this way. Figure 6 shows the addition of a diagnostic test to our previous example. In ordinary clinical practice such exhaustive data may not be available and it may be necessary to act on incomplete knowledge. Whenever possible, this should be done in such a way as to accumulate the necessary information so that future patients may benefit from the knowledge gleaned from current practice.

Occasionally a diagnostic test or procedure can be performed on an unselected population, for example the use of routine ultrasound examination designed to examine the fetal skull and spine with a view to identifying anencephaly and spina bifida directly. In this case the procedure is being applied as if it were a screening test even though it is performed to make a diagnosis. It is, effectively, a screening and diagnostic test combined and will need to be assessed as such, comparing its performance with the alternative sequence of screening and diagnostic tests available.

The checklist

Table 1 shows the checklist which brings together the questions we have discussed that authors will need to consider in reporting on the performance and value of screening and diagnostic tests. It does not cover the assessment of screening tests for chronic disease since the performance of the test cannot be distinguished from the effect of treatment. Such a test cannot therefore be assessed alone. It does, however,

Table 1. Checklist for the assessment of screening or diagnostic tests

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The test

1. Is the test a screening test or a diagnostic test?
2. Is it one of several tests or enquiries?
3. If so, are the tests carried out in series (e.g. only those whose first result is positive have a second test and so on) or in parallel (everyone has all tests)?

The disorder

4. What is the disorder that the test is designed to detect?
5. Can the disorder be defined without reference to the test?
6. What is its natural history?
7. Is the natural history of those with positive tests similar to the natural history of those with negative tests?

Prevalence of the disorder

8. What is the prevalence of the disorder in the population to be tested?
9. What method was used to determine prevalence?

Therapeutic intervention

10. If it is a screening test, what diagnostic test will follow and what therapeutic intervention if that test is also positive?
11. If it is a diagnostic test, what therapeutic intervention will follow a positive result?
12. What is the justification for this therapy?

Test results

13. Is the test or enquiry quantitative or qualitative?
14. If it is quantitative (e.g. maternal serum AFP level) what is the distribution of screening test results in affected and unaffected subjects?
15. If it is qualitative (e.g. cervical smear test) what are the possible definitions of a positive result?

Test performance

16. What is the detection rate?
17. Has this been determined from a complete series of affected individuals in which any with negative results were not overlooked?
18. What is the false-positive rate?
19. What are the odds of being affected given a positive result? How will this vary according to the prevalence of the disorder?
20. For quantitative tests, what is the effect of changing the cut-off level on the detection rate, false-positive rate and the odds of being affected given a positive result?
21. Can a flow diagram be constructed starting with 100 000 individuals and ending with the final outcome, segregating affected from unaffected at the outset?

Cost and benefit analysis

22. What are the medical costs and benefits?
23. What are the financial costs and benefits?
24. Can a balance sheet be drawn up for each, including any suffering that will be alleviated through the application of the whole testing process and at what cost and medical intervention?

Evaluation of the tests

25. Is the test better than other tests when comparison is made of their respective detection rates and false-positive rates?
26. Does it offer an advantage over other tests to such an extent that it should replace an existing test or be added to it and used in combination?

Practical problems

27. What are the practical problems in implementing the test as a screening or diagnostic procedure?
28. Are special facilities required?
29. If so, what is their availability or ease of installation?

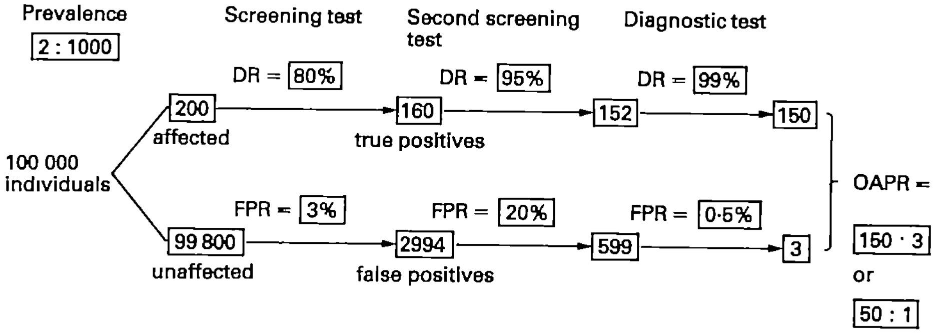

Fig. 6. Flow diagram as in Fig. 3 with the addition of a diagnostic test performed on individuals with positive first and second screening tests. The test has a detection rate (DR) of 99% and a false-positive rate (FPR) of 0·5%. OAPR=odds of being affected given a positive result.

cover many of the tests conducted in obstetric practice, particularly those used for prenatal diagnoses.

When there are existing tests that can be used to detect the same disorder as the test that is being reported it is necessary to include a comparison of their performance (Questions 25 and 26). We have also included in the checklist questions relating to the application of the test in practice (Questions 27–29). This aspect can easily be taken for granted and the practical problems underestimated. Although this does not readily lend itself to quantification it should, nonetheless, be explicitly considered.

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Reporting controlled trials

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The aim of this short paper is to make it easier for authors, referees, editors and, ultimately, readers to assess the quality of controlled trials mounted to compare alternative forms of care. The guidelines set out below are based on checklists published in other journals (e.g. the *British Medical Journal* 1987), and schemes suggested for assessing the quality of published randomized controlled trials (Mahon & Daniel 1964; Mosteller *et al.* 1980; McMaster University Department of Clinical Epidemiology and Biostatistics 1981; Chalmers *et al.* 1981; Der Simonian *et al.* 1982; Zelen 1983; Emerson *et al.* 1984; Thacker 1985; Meinert 1986). The rationale for paying attention to aspects of study design and reporting is discussed in these and other publications included in the bibliography (see Grant & Chalmers 1985; Chalmers 1989).

A list of 28 reasonable questions to ask in respect of reports of controlled trials is presented in Table 1. Not all of these questions are relevant to all trials. Nevertheless, evidence that investigators have paid appropriate attention to these guidelines is likely to improve the chances that a trial report submitted to this Journal will be accepted for publication.

Introduction to the report

Some of the questions, such as whether there has been a clear statement of the rationale for and the objective(s) of a controlled trial (Question 1), may seem hardly worth asking; yet it is surprising how often the objectives of studies are not clearly stated in manuscripts and even published reports.

Description of materials and methods

The answers to questions about the materials and methods used in controlled trials must be clear if readers are to judge how much faith to place in the results presented. Questions 2–13 deal with the most important of these issues. A common controversy associated with controlled trials is the area of clinical practice to which the results of a trial can be generalized. There must, therefore, be a clear description of the source of the study participants (Question 2) and of the entry and exclusion criteria (Question 3). In some trials it is possible to describe people who met the entry criteria but who did not join the study. This information can be useful for assessing whether those who joined the trial are systematically different from those who did not.

Two factors which may influence recruitment to a trial are the method of approach to and the information given to potential participants (Question 4). There are differences of opinion about the nature and timing of consent to participation in a trial and they will obviously vary depending on the nature of the trial; both should be outlined in the report.

Random allocation is the only strategy for eliminating biased treatment assignment in controlled trials. Some methods of 'random' assignment are more prone to corruption than others (Chalmers *et al.* 1983). Methods of assignment which allow identification of the treatment before formal trial entry—for example, alternate allocation, or case note numbers, or date of birth—are much less satisfactory than methods which require formal registration of entry before random allocation of treatment. This is the reason why a brief description of the actual way in which the treatments were assigned is essential (Question 5). Knowledge of the treatment allocation by either the subject or the investigator may also change the intervention (Spriet & Simon 1985)—see below. Chance imbalances in important prognostic variables, a problem which

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Table 1. A checklist for reports of controlled trials

Introduction to the report

1. Is there an adequate description of the rationale for and objective of the trial in terms of hypothesized effect(s) of specific interventions?

Description of materials and methods

2. Is there an adequate description of the source of participants (hospital, outpatient clinic, etc.) and the timing and duration of recruitment?
3. Is there an adequate description of the entry and exclusion criteria?
4. Has the method of approach to potential participants and the information given to them been described?
5. Is there a satisfactory description of the actual way in which the treatments were assigned, and the use of prognostic stratification, if any?
6. Have the forms of care compared (the treatment regimens), both experimental and control, been described in sufficient detail to allow replication?
7. Has the degree of masking ('blinding'), if any, of participants and investigators been described?
8. If a placebo was used, was there an assessment of its success in 'masking' the nature of the treatment?
9. Have the methods used to measure outcome been described, specifying whether or not the assessor knew the treatment allocation ('degree of masking')?
10. Has the objective been specified in terms of a quantified effect on a defined primary measure of outcome?
11. Is there an explanation of how the final sample size was chosen and a statement on statistical power in respect of the quantified effect on the primary measure of outcome?
12. If there were any interim analyses, have the arrangements and methods used been described?
13. Have all the statistical methods been identified and is there a description of any statistical techniques used which are not in common use?

Presentation of results

14. Have the total numbers of participants entered into each of the comparison groups been presented?
15. Have the characteristics of the groups at entry been tabulated so that their comparability can be checked?
16. Has the extent of adherence to study regimens (numbers completing treatment, numbers complying with regimen, numbers 'crossing-over' to receive treatment opposite to that allocated—'contamination') been reported satisfactorily, for each trial group separately?
17. Have the reasons for withdrawals been reported, for each trial group separately?
18. Has the comparability of the trial groups in respect of other relevant treatments (co-interventions) been described?
19. Have the primary analyses been based on all subjects as allocated, i.e. on 'intention-to-treat', with non-compliers and 'crossovers' retained in the group to which they were originally assigned?
20. Have the estimated sizes of any differential treatment effects been accompanied by confidence intervals?
21. Have complications and side-effects been reported, for each trial group separately?
22. Have the implications of any imbalances in prognostic variables been considered?

Study conclusions

23. Have the conclusions been based on the analysis?
24. Have competing explanations for the study outcome been discussed and, where appropriate, explored in additional statistical analyses?
25. Has the statistical power of the completed study to detect or rule out differences been discussed?
26. Has a distinction been drawn between prior hypotheses and *post hoc* findings which were not prespecified?
27. Have the study results been placed in the context of existing findings?
28. Have the implications for clinical practice and future research been spelled out?

is more common in small trials, may be protected against by prognostic stratification (Pocock 1983; Meinert 1986) and, if so, this should be described (Question 5).

If the reported results of an evaluation of alternative forms of care are to be of use to its readers, the forms of care compared must be described in sufficient detail to allow the results of the study to be implemented in clinical practice or replicated in a further study (Question 6).

Knowledge of the treatment to which a participant has been allocated may lead to imbalance in other treatments ('co-intervention') by investigators, to psychologically mediated effects of care in participants, and to biased observations by those assessing the outcomes of treatment. For these reasons the extent of masking ('blinding') of participants, investigators and outcome assessors should be described (Questions 7, 8, 9). Liability to biased assessment of outcome also depends on what measurement is being used. Unambiguous measures such as death and caesarean section are less prone to bias than 'softer' measures (Thacker 1985).

The objective of a controlled trial should be specified in terms of a quantified effect on a defined primary measure of outcome (Question 10). The importance of statistical power to identify such an effect is often not sufficiently appreciated (Freiman *et al.* 1978; Detsky & Sackett 1985) when evaluating a sample size in a randomized controlled trial (Question 11). There are two major problems with trials in which the sample size is too small. Firstly, they tend falsely to ascribe real differences between treatments to chance (Type II error—Freiman *et al.* 1978). Secondly, they may grossly overestimate the true effect of an intervention when the difference observed in the trial is statistically significant. A full discussion of sample size is available elsewhere (Pocock 1983; Meinert 1986).

The use of multiple tests of statistical significance increases the risk of falsely claiming that an observed difference is real when, in truth, it solely reflects chance (Type I error) (Pocock *et al.* 1987). Interim analyses or analyses involving multiple end-points (Question 12) therefore carry this risk unless appropriate corrections are made (Pocock 1983).

All statistical methods should be identified and unusual techniques should be described in sufficient detail to allow their replication (Question 13).

Presentation of results

Description of the trial groups at entry (Questions 14 and 15), with tabulation of the major prognostic variables, should provide reassuring evidence that the allocation was indeed random. It also allows a check that the groups do not differ importantly in one or more prognostic variables.

Non-compliance, crossover to receive the alternative treatment ('contamination'), and imbalance in other treatments ('co-interventions') may all alter the nature of the interventions being compared (Questions 16, 17, 18).

It is comparison of the groups characterized by the random treatment allocation at entry which is free of selection bias (provided that treatment assignment was truly randomized). Withdrawals after entry, particularly if they differ between the groups, or the reasons are related to a specific treatment, may introduce selection bias (Gail 1985); the likely extent of this can only be assessed if the number and reasons for withdrawals are listed for each trial group separately (Question 17). This is the basis for recommending that primary analyses should be based on the groups as allocated (Question 19), regardless of subsequent management ('intention-to-treat' analyses). The manoeuvres compared in an 'intention-to-treat' analysis are thus the actual managements used in the trial (Questions 16 and 18), rather than the strict study regimens (Question 6). A possible exception to the rule about 'intention-to-treat' primary analyses is the explanatory trial (Schwartz *et al.* 1980), a small, tightly controlled trial in an ideal 'laboratory-type' setting. Even in these circumstances an 'intention-to-treat' analysis can be helpful to assess the likely size of any bias due to withdrawals.

Most comparisons of trial groups are better presented as estimations of a treatment effect (e.g. differences in means for continuous variables, odds ratios or relative risks for categorical data), with confidence intervals, than as a test of a hypothesis by generation of a *P* value (Gardner & Altman 1986) (Question 20). These estimations should be presented.

The outcomes assessed should include possible side-effects and complications (Question 21).

It may seem sensible to adjust for chance imbalances in prognostic variables in secondary analyses after the trial is completed (Question

22). These secondary analyses should be used to check whether the imbalance makes any important difference to the conclusions drawn from the study.

Study conclusions

Questions 23–28 concern the validity of the conclusions based on the analyses presented in the report. It goes without saying that these should be supported by the data presented (Question 23) and that a range of possible interpretations of the results of the controlled trial should have been considered (Question 24). If no clear difference is observed between the trial groups there should be comment (Question 25) on the statistical power of the study to detect or rule out the differences which were prespecified in the trial's objectives (Detsky & Sackett 1985).

Post hoc findings which are 'statistically significant' should be given much less weight than prespecified hypotheses which are supported by a statistically significant difference (Question 26).

Finally, it is important that the results of the study should be placed in the context of existing findings (Question 27), and that the implications for clinical practice and future research should be spelled out (Question 28).

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Antenatal administration of betamethasone to prevent respiratory distress syndrome in preterm infants: report of a UK multicentre trial

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Summary. In a prospective, randomized, double-blind, multicentre trial the effect of antenatal treatment with betamethasone phosphate was compared with placebo in the prevention of the respiratory distress syndrome (RDS) in preterm infants. The dose of betamethasone was 4 mg every 8 h for six doses, unless delivery occurred. The 251 women who were enrolled gave birth to 262 liveborn infants, 130 in the betamethasone and 132 in the placebo group; the two groups were evenly matched in most respects. The diagnosis of RDS in the newborn was confirmed by two independent assessors. Seven of the 130 infants in the betamethasone group and 16 of the 132 in the placebo group developed RDS. In infants whose mothers had received at least three injections, RDS was also less frequent in the steroid group than in the placebo group (3/104 and 10/104 respectively; $P<0.05$). There was a significant reduction of RDS in those born between 24 h and 6 days after entry into the trial (0/30 and 8/45 respectively; $P<0.05$). The largest difference in frequency of RDS occurred in the subgroup of infants born before 34 weeks gestation, within 8 days of trial entry, and whose mothers had received at least three injections (0/27 steroid group and 7/32 placebo group; $P=0.03$), and there were also significantly fewer neonatal deaths (2/27 and 13/32, respectively; $P<0.01$) in this subgroup. Betamethasone did not provoke earlier delivery. Premature rupture of the membranes and maternal hypertension did not seem to contraindicate the use of steroids: there was no increase in maternal or neonatal sepsis nor in stillbirth in hypertensive pregnancies in the steroid group. Neonatal jaundice was significantly less frequent in the steroid (55/129) than in the placebo group (81/127; $P<0.01$) but not in the subgroups born before 34 completed weeks gestation.

The respiratory distress syndrome (RDS) resulting from surfactant deficiency in the lungs of the newborn baby occurs in 10–15% of infants weighing less than 2500 g at birth (Avery 1981). Infants weighing less than 1500 g and those below 30 weeks of gestation are most susceptible to the disorder and are most likely to die from it (Roberton 1982). Although treatment of RDS is improving and survival is increasing, the disease remains a severe problem in the smallest preterm infant when preterm delivery cannot be

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prevented or has to be induced. Therefore, methods of preventing RDS or of ameliorating its severity are still required.

Liggins (1969) reported that glucocorticoid infusion in pregnant ewes, given to induce preterm delivery, improved fetal lung stability. The subsequent clinical trial, designed to investigate the effect of betamethasone on RDS in preterm infants, was reported by Liggins & Howie (1972). There was a significant reduction in the frequency of RDS in the betamethasone group compared with the control group, particularly in those infants born between 24 h and 7 days after entry to the trial. In 1974 a group of obstetricians and paediatricians in the UK initiated a randomized double-blind collaborative study to determine the advantage, if any, of betamethasone therapy in pregnant women at risk of preterm delivery and to determine whether Liggins' data could be confirmed.

Patients and methods

At each of the 11 participating hospitals, the recruitment of subjects and project supervision was undertaken jointly by one paediatrician and one obstetrician. Each hospital obtained approval from the relevant ethics committee before being enrolled as a collaborating centre, and all women gave informed consent to their participation in the study.

Patients were eligible for the study if the length of gestation was judged by the obstetrician to be less than 34 completed weeks and either the woman was apparently in spontaneous labour, or required preterm delivery for obstetric or medical reasons. Patients were not included if corticosteroids were contraindicated on medical grounds, if a delay of ≥24 h before delivery was judged to be against fetal or maternal interests, if diabetes was present or intrauterine infection was suspected. However, multiple pregnancy, hypertension (blood pressure ≥140/90 mmHg), oedema, proteinuria and rhesus incompatibility were not contraindications for entry to the study.

Drugs and dosage

This double-blind, parallel group study compared betamethasone and placebo randomized in small blocks so that each participating hospital had a similar distribution of active drug and placebo. Patients received either 4 mg betamethasone as the phosphate ester (subsequently referred to as betamethasone), or a placebo (the vehicle). Intramuscular injections of 1 ml were given every 8 h for a maximum of six doses. Only one course of injections was given to each participant, irrespective of the subsequent course of the pregnancy.

All the women in spontaneous labour received an intravenous infusion of salbutamol as a tocolytic, according to a standard schedule. The end-point was determined by the woman's response. Antibiotics were not administered routinely for prolonged rupture of the membranes.

Clinical information

Information about the participants included the following details.

Pregnancy. Length of gestation calculated both from the first day of the last menstrual period and from the obstetrician's assessment; history of smoking, oral contraception, drugs in pregnancy and any complications of pregnancy.

Labour and delivery. Time and duration of ruptured membranes before delivery, factors predisposing to preterm labour, evidence of intrauterine infection, drugs given during labour, duration of labour and delivery, presentation and method of delivery.

All infants were examined clinically after birth. The time to cord clamping was recorded, as were Apgar scores at 1 and 5 min, any resuscitation employed, body temperature and time on arrival at the nursery, and clinical evidence of intrauterine infection. The subsequent results of bacteriological culture of specimens from various sites, hypoglycaemia (<1·4 mmol/l), its duration and timing, any clinically apparent jaundice, the highest serum bilirubin concentration and its time after birth, and all drugs given in the first 48 h were recorded. Gestational age was assessed, if possible, at 1 to 2 days after birth, using the scores developed by Dubowitz *et al.* (1970) or Farr *et al.* (1966). For infant deaths, the time and cause of death and any autopsy findings were noted.

Respiratory distress syndrome (RDS)

In the first 4–24 h after birth, the presence of signs of respiratory distress was recorded as well

Table 1. Details of women at trial entry

Variable	Betamethasone (n=126) n (%)	Placebo (n=125) n (%)
Multiparae	47 (37·3)	50 (40·0)
Surgical induction	7 (5·6)	5 (4·0)
Spontaneous premature labour	119 (94·4)	120 (96·0)
Membranes		
Spontaneous rupture	35 (27·8)	43 (34·4)
Intact	73 (57·9)	75 (60·0)
Not known	11 (8·7)	2 (1·6)
Oedema	8 (6·3)	4 (3·2)
Proteinuria (no infection)	7 (5·6)	3 (2·4)
Blood pressure ≥140/90 mmHg	12 (9·5)	6 (4·8)
Interval between trial entry and delivery (h)		
<24	31 (24·6)	30 (24·0)
24–47	6 (4·8)	17 (13·6)
48–95	10 (7·9)	13 (10·4)
96–143	7 (5·6)	6 (4·8)
144–168	3 (2·4)	2 (1·6)
>168	69 (54·7)	57 (45·6)

as the maximum respiratory rate, Pa_{O_2}, Pa_{CO_2}, arterial pH and the timing of each; all babies with respiratory problems also had a chest radiograph. Criteria for the diagnosis of idiopathic RDS included the persistence for >6 h of respiratory distress including flaring of the nostrils, grunting, rib recession and tachypnoea (≥60 breaths/min), central cyanosis and need for supplemental oxygen.

A characteristic chest radiograph demonstrating diffuse fine granularity, a positive air bronchogram and small volume lungs were preferred for confirmation of the diagnosis. Respiratory distress was graded in severity as mild (requiring a fractional inspired oxygen concentration [FiO_2] of ≤0·4), moderate (requiring an FiO_2 of >0·4 and ≤0·8) and severe (requiring an FiO_2 >0·8 and/or ventilatory support).

After completion of the trial all hospital records of infants who had developed any respiratory problem were reviewed by one of two expert independent assessors (E.O.R.R. or C.R.W.) who did not know which treatment the mother had received. In addition, the two assessors studied the case notes, chest radiographs and autopsy reports of all neonatal deaths to determine which of them had RDS. The records were reviewed in a batch to ensure that the same diagnostic criteria were applied to them all.

Statistical analysis

All mean values are quoted with 1 standard deviation. The data were analysed using the χ^2-test with Yates' correction for continuity if appropriate, unless the usual criteria for this test were not met, in which case Fisher's exact test was used. The level of statistical significance was set at P=0·05. Further information is provided by the mean percentage difference and its 95% confidence interval (CI).

Results

Maternal demographics and delivery

The trial started in mid-1975 and continued until February 1978; 251 women were recruited of whom 126 received betamethasone and 125 the placebo. The two groups were similar in most respects, including the use of oral contraceptives before pregnancy and drugs during pregnancy. Salbutamol was given to 116 receiving betamethasone and to 117 in the placebo group. Oxytocin, however, was administered to significantly more women in the betamethasone group (12) than in the placebo group (3), observed difference 7·1% (95% CI 1·3% to 12·9%; P<0·05).

Gestation at entry to the trial ranged from 24 to 37 weeks in both the betamethasone and the placebo groups (mean 31·5, SD 2·5 and 31·4, SD

Table 2. Details of infants in the two groups

Variable	Number of infants Betamethasone (n=131)	Placebo (n=137)	Total (n=268)
Livebirths			
Males	72	84	156
Females	58	48	106
Stillbirths	1	5	6
Apgar score			
1-min, no. recorded	129	132	261
Median score	8	7	
Interquartile range	5–9	5–9	
5-min, no. recorded	127	122	249
Median score	9	9	
Interquartile range	8–10	8–10	
Time to cord clamping (min)			
≤1	101	110	211
>1	23	22	45
Not known	6	0	6
Temperature			
No. recorded	91	98	189
Mean (°C)	35·7	35·8	
No. <35°C	20	21	41
Clinical jaundice			
Present	55	81	136
Absent	74	46	120
Not known	1	5	6

2·7 weeks respectively). Gestational age assessed from the date of the last menstrual period, obstetric assessment of fetal size and, later, paediatric assessment, showed good agreement in most cases. For 10 betamethasone- and 11 placebo-allocated women, gestation at entry to the trial was found to be in excess of 34 weeks when gestational age was assessed after birth, although when recruited they were thought to be <34 weeks. Babies born before 34 weeks were analysed separately for RDS and neonatal mortality.

Most of the women were apparently in spontaneous preterm labour when admitted to the trial (Table 1) and predisposing factors included urinary tract infection in 27, antepartum haemorrhage in 31 and cervical incompetence in 27, all of which were well balanced between the two groups. There were no significant differences in the number of women with clinical oedema or proteinuria, nor in the mean blood pressure or frequency of hypertension. In six patients in each treatment group, intrauterine infection was diagnosed before delivery, and was subsequently confirmed bacteriologically in seven.

In 61 women (24%), the interval between trial entry and delivery was <24 h and 126 were delivered more than 7 days after entry to the trial (Table 1). Betamethasone treatment did not shorten the interval between trial entry and delivery: the mean intervals were 21·9 days in the betamethasone group and 15·8 days in the placebo group.

Some women did not receive the full course of six drug injections because of early delivery. Most women received at least three injections including 101 in the betamethasone group and 100 in the placebo group. All six injections were given to 82 women in the betamethasone group and 77 in the placebo group.

The duration of labour was markedly similar in the two groups; it lasted <12 h for 74% of livebirths in the betamethasone group and for 73% in the placebo group. Most women were delivered vaginally and the presentation and mode of delivery were similar in the two groups. In particular, there was no significant difference in the total number of caesarean sections between the betamethasone and placebo groups (7% and 12% of livebirths respectively).

Neonatal data

There were five sets of twins in the betamethasone group, and 10 sets of twins and one set of triplets in the placebo group, so the numbers of infants born were 131 and 137 respectively, of which 130 and 132 respectively were born alive. None of these differences is statistically significant. Male infants predominated in both groups; the higher proportion of males in the placebo group than in the betamethasone group was not statistically significant, with an observed difference of 8·2% (95% CI 3·6% to 20·1%). There were no differences in the frequency of asphyxia, methods of resuscitation, time to cord clamping or initial body temperature (Table 2). The birthweights ranged from 609 to 4100 g in the betamethasone group and from 500 to 4020 g in the placebo group with mean values of 2203 g (SD 757) and 2133 g (SD 753) respectively.

Clinical signs of jaundice were observed in significantly more babies in the placebo than in the betamethasone group; observed difference 21·1% (95% CI 9·2% to 33·1%; P<0·01). Bilirubin tended to be measured in more babies in the placebo group (58%) compared with the betamethasone group (42%), although the mean maximum bilirubin concentrations, and the times after birth when they were measured, did not differ significantly between the two groups.

A few babies in each group had a low capillary test strip blood glucose after birth. Blood glucose concentration was measured in only nine babies from each group, at mean ages of 24 h in the betamethasone and 9 h in the placebo group with mean levels of 1·9 and 2·3 mmol/l respectively. Clinical signs of infection were present in 11 infants, seven of whom were in the placebo group. There were seven positive cultures from ear and nasal swabs or gastric aspirates in the betamethasone group and 13 in the placebo group, with an associated increased use of antibiotics in the placebo group. None of these differences was statistically significant.

The range for gestation at delivery, 24–41 weeks, was identical for the two groups. The mean gestation at delivery of all births, as judged from maternal dates only, was 34·6 (SD 3·8) weeks in the betamethasone and 33·5 (SD 4·2) weeks in the placebo group (mean difference 1·1 weeks, 95% CI 0·3 to 1·9 weeks; P<0·05).

Influence of gestation and birthweight on frequency of RDS

Twenty-three babies with signs of respiratory difficulty and tachypnoea were judged by the independent assessors to have RDS: seven (5·4%) were in the betamethasone group and 16 (12·1%) in the placebo group (Table 3). Four babies in each group could not be assessed for lack of information.

All seven babies with RDS in the betamethasone group had at least three signs of respiratory difficulty, five had characteristic radiographic

Table 3. Proportion of livebirths developing respiratory distress syndrome in various subgroups according to treatment

			Difference (%)		
Subgroup	Betamethasone	Placebo	Observed	(95% CI)	P
Overall	7/130	16/132	6·7	(−0·05 to 13·5)	NS
Birthweight (g)					
<1500	3/23	8/29	14·5	(−6·8 to 35·9)	NS
≥1500	4/107	8/103	4·0	(−2·3 to 10·3)	NS
Gestation <34 weeks	5/99	14/101	8·8	(0·8 to 16·8)	<0·05
At least three injections	3/104	10/104	6·7	(0·2 to 13·2)	<0·05
+ delivery within 6 days	0/30	8/45	17·8	(16·7 to 18·9)	<0·05
+ delivery within 14 days	1/44	10/61	14·1	(3·8 to 24·4)	<0·05
+ delivery within 21days	3/51	10/70	8·4	(−2·0 to 18·9)	NS
+ delivery within 8 days plus gestation <34 weeks	0/27	7/32	21·9	(7·6 to 36·2)	0·03

changes and five required respiratory support. In the placebo group, seven of the 16 babies with RDS had at least three signs of respiratory difficulty, and another three required ventilatory support from birth. Of the remaining six babies, four had chest radiographs characteristic of RDS, and three of these, with severe disease, died. Two babies had mild distress and tachypnoea, but were judged by the assessors to have RDS. The difference in the frequency of RDS between the two treatment groups was not statistically significant (Table 3).

Influence of number of injections and interval between trial entry and delivery on frequency of RDS

The data for infants born to mothers who received at least three injections of trial drugs were analysed separately because of the uncertainty of whether only one or two injections would have much influence on outcome. In this group of 208 liveborn infants, 13 babies developed RDS, three in the betamethasone (2·9%) and 10 in the placebo group (9·2%) (Table 3). The occurrence of RDS was also correlated with the interval between first injection and delivery (Fig. 1) in order to test the report by Liggins & Howie (1972) that the maximum benefit of therapy occurred in infants born between 24 h and 7 days of trial entry. The 95% CI of the differences between the two groups remained in favour of betamethasone for at least 2 weeks.

There were no babies with RDS in the betamethasone group born within 6 days of trial entry compared with eight babies with RDS in the placebo group. This difference is statistically significant (Table 3). In infants born within 14 days of trial entry, there were also significantly fewer with RDS in the betamethasone group. Mean gestation at trial entry of the infants born within 6 days and those born within 14 days of trial entry was very similar in the two groups, namely 31·6 and 31·3 weeks in the steroid group respectively, and 31·4 and 31·6 weeks in the placebo group.

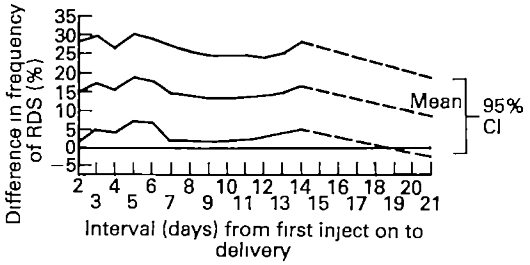

Fig. 1. Cumulative differences in frequency of RDS between betamethasone and placebo groups during the first 3 weeks after trial entry—all livebirths to mothers who had received at least three injections. A positive difference favours betamethasone. Mean difference shown by middle curve; 95% confidence interval (CI) by outer lines.

For the infants whose mothers had received at least three injections, the influence of the interval between trial entry and birth was also analysed for the subgroup of infants born before 34 completed weeks gestation.

The most significant difference in the frequency of RDS between the two groups was observed in babies born within 8 days of trial entry (betamethasone 0 of 27, placebo 7 of 32; Table 3).

Mortality

There were 40 deaths (14·9%) of which 15 occurred in the betamethasone group and 25 in the placebo group (Table 4). They consisted of six stillbirths (2·2%), 28 early neonatal deaths (14 in each group), three late neonatal deaths (all in the placebo group) and three post neonatal deaths at 30, 35 and 127 days (all in the placebo group). The perinatal mortality was 12·7% and the overall mortality amongst livebirths was 13·0%. Congenital abnormality was present in four deaths in the betamethasone group, but in none in the placebo group. If these four deaths are excluded the perinatal mortality in the betamethasone group falls to 8·4% and the mortality for livebirths falls to 7·7%.

In the placebo group, RDS was considered to be the main cause of death in three infants and the major contributory cause in a further five infants. In the betamethasone group there were three deaths in which RDS was a major contributory cause of death (Table 4).

In the babies born before 34 completed weeks, neonatal mortality was 15·5% (31 of 200); 11·1% in the betamethasone group and 19·8% in the placebo group.

None of these differences was statistically significant nor when they were analysed separately for infants weighing <1500 g at birth. However, a highly significant difference in mortality was seen in that subgroup of babies whose mothers received at least three injections and who were

Table 4. Mortality rates in various subgroups according to treatment

Group or subgroup	Betamethasone (%)	Placebo (%)	Difference (%) Observed	(95% CI)	*P*
Total population	15/131 (11·4)	25/137 (18·2)	6·8	(−4·7 to 12·2)	NS
Excluding stillbirths	14/130 (10·8)	20/132 (15·2)	4·4	(−3·7 to 12·5)	NS
Plus excluding lethal abnormalities	10/130 (7·7)	20/132 (15·2)	7·5	(−0·2 to 15·1)	NS
Perinatal mortality	15/131 (11·5)	19/137 (13·9)	2·4	(−5·6 to 10·4)	NS
Neonatal deaths	14/130 (10·8)	17/132 (12·9)	2·1	(−5·7 to 9·9)	NS
With RDS	3/130 (2·3)	8/132 (6·1)	3·8	(−1·1 to 8·6)	NS
Gestation <34 weeks	11/99 (11·1)	20/101 (19·8)	9·7	(−0·4 to 19·7)	NS
At least three injections + gestation <34 weeks + delivery within 8 days	2/27 (7·4)	13/32 (40·6)	32·2	(13·5 to 52·9)	<0·01

born before 34 weeks gestation and within 8 days of trial entry (Table 4).

Infection was found to be a major contributory cause of death in nine infants, two in the betamethasone group and seven in the placebo group (Tables 5 & 6).

Discussion

The antenatal administration of steroids for the prevention of RDS has been extensively reviewed (Papageorgiou & Stern 1986). Most reports confirm a reduction in the frequency of

Table 5. Details of babies developing respiratory distress syndrome (RDS) according to treatment

Birthweight (g)	Gestation at birth (weeks)	Sex	Outcome	Cause(s) of death other than RDS
Betamethasone				
860	29	F	Died 49 h	IVH
1080	28	F	Died 7 h	IVH
1130	30	F	Died 28 h	Pneumothorax, subarachnoid haemmorrhage
1720	31	F	Survived	
1800	36	M	Survived	
1840	33	M	Survived	
2620	35	M	Survived	
Placebo				
860*	28	M	Died 360 h	IVH, pneumonia
870*	28	M	Died 36 h	IVH
1000	29	F	Died 34 h	—
1020*	27	F	Died 144 h	Twin/twin transfusion, kernicterus
1020	28	F	Died 12 h	—
1240	29	M	Died 672 h	Patent ductus arteriosus
1820	31	M	Died 12 h	IVH
1970	32	M	Died 18 h	IVH, coagulopathy
1240	28	M	Survived	
1400	30	M	Survived	
1560	34	M	Survived	
1850	33	M	Survived	
1960	32	M	Survived	
2180	33	M	Survived	
2310	32	M	Survived	
2340	34	M	Survived	

*Twin.

IVH, Intraventricular haemorrhage.

Table 6. Deaths of liveborn infants other than those due to respiratory distress syndrome

Birthweight (g)	Gestation at birth (weeks)	Sex	Age at death (h)	Main cause(s) of death
Betamethasone				
720	26	F	51	Prematurity
720	29	M	12	Prematurity, aponea, hypothermia
840	27	M	12	Prematurity
1000	28	F	72	Prematurity
1131	28	M	5	Tentorial tear, cerebral haemorrhage
1400	29	M	1	Intrapartum hypoxia
1640	31	F	168	Multiple abnormalities, infection
1740	34	F	16	Diaphragmatic hernia, VSD
1820	33	F	14	Asphyxia, meconium aspiration
2150	34	F	14	Pneumonia, multiple abnormalities
2320	34	M	24	Meningomyelocoele, hydrocephalus
Placebo				
790*	28	M	3048	Meningitis, PDA
810†	27	F	42	Prematurity
NK†	27	M	4	Prematurity
830†	27	F	720	IVH, pneumonia, BPD
960	26	F	12	IVH
1200	30	M	840	Infection, subarachnoid haemorrhage
1215	29	M	2	Prematurity
1220	29	F	29	Infection, ischaemia of leg
1360	28	M	271	Pneumonia, renal failure
1450	30	M	14	IVH
1640	32	M	72	IVH, meningitis
1740	31	F	22	Septicaemia

*Twins.

†Triplets

NK, Not known; IVH, intraventricular haemorrhage; VSD, ventricular septal defect; BPD, bronchopulmonary dysplasia; PDA, patent ductus arteriosus.

RDS, but not its complete elimination. Since the original observations by Liggins & Howie (1972) their cohort of women has been increased (Liggins 1977) and an increased dose of betamethasone investigated, without showing additional benefit. Most later investigators have used phosphate and acetate esters of betamethasone, although dexamethasone, betamethasone phosphate alone, prednisolone and hydrocortisone have also been used. The dosage, frequency and routes of administration of glucocorticoids have varied, but in most trials an attempt has been made to continue treatment for 48 h. Various tocolytic agents have been used to delay delivery in unplanned preterm labour.

The UK Multicentre Collaborative Trial employed betamethasone phosphate as the active glucocorticoid, its inert vehicle for the placebo, and only one tocolytic agent, salbutamol. Acknowledged experts made the final diagnosis of RDS at the end of the study unaware of the treatment given. There were fewer babies with RDS in the betamethasone group; the difference was statistically significant in the subsample of women who had received at least three injections and were delivered within 6 or 14 days of trial entry, mainly due to those delivered before 34 completed weeks gestation. These results are in agreement with many other studies which have demonstrated that for maximum protection against RDS, at least 24 h and preferably 48 h should elapse between the start of steroid treatment and delivery. The results also support previous trials which showed that antenatal steroids exert their greatest effect if given before 34 weeks gestation (Morrison *et al.* 1978; Papageorgiou *et al.* 1979). A recent report (Kwong & Egan 1986) confirmed a beneficial effect in infants between 24 and 28 weeks gestation.

Neither the severity of RDS nor the overall number of deaths resulting from it differed significantly between the two study groups. Although not all studies have shown a significant effect of steroids on neonatal mortality, there were significantly fewer deaths in babies born within 8 days of their mothers receiving at least three injections of betamethasone, largely due to a reduction in deaths in those <34 weeks gestation.

Twins constituted 7·6% of the liveborn infants in the betamethasone group but none had RDS, while in the placebo group 23 infants were multiple births (17·4%) and two had RDS. Thus, this trial is inconclusive about the prophylactic effect of glucocorticoids only being exerted on singleton births (Collaborative Group on Antenatal Steroid Therapy 1981).

Although a recent report has shown antenatal betamethasone to be effective in the presence of premature rupture of the membranes (Morales *et al.* 1986), whether premature rupture of the membranes helps to prevent RDS and whether antenatal glucocorticoids confer any additional benefit remain controversial. For the patients given at least three injections in the UK trial, 1 of 26 offspring in the betamethasone group developed RDS in spite of prematurely ruptured membranes, compared with 3 of 20 in the placebo group.

The UK trial demonstrated less clinical jaundice, and hence fewer bilirubin determinations in the betamethasone group. The reasons for this apparent effect are unclear and this finding has not been reported previously.

Most investigators have found no increase in maternal or neonatal sepsis; this was the finding of the UK trial, in which sepsis occurred less often in the betamethasone group.

The initial trial in New Zealand (Liggins & Howie 1972) suggested that severe hypertension with oedema and severe proteinuria was associated with increased risk of fetal death in pregnancies treated with glucocorticoids; subsequently the critical factor was thought to have been inordinate delay in delivery. In the 18 women with hypertension in the UK trial there were no stillbirths but two neonatal deaths. No RDS occurred in the betamethasone group but one neonatal death and one baby with RDS occurred in the placebo group.

Both betamethasone and dexamethasone cross the placenta readily and have a similar affinity for the cells of human fetal lungs (Ballard 1977). Betamethasone was the most potent at inducing surfactant in the rat (Anderson *et al.* 1981) and the human (Block *et al.* 1977; Schmidt *et al.* 1984). The mechanism of action of antenatal glucocorticoids in protecting against RDS is not only to increase synthesis of surface active material in the lung; the collagen/elastin ratio is also altered (Johnson *et al.* 1981). In animals, glucocorticoids cause greater lung distensibility, increased deflation stability, increased narrowing of septa and more alveolarization (Kessler *et al.* 1982).

In the UK trial RDS was reduced in frequency, but occurred in seven babies despite betamethasone. However, only one of the seven mothers had all six injections and was delivered within 8 days of inclusion into the trial; four had fewer than three injections, and the other two were delivered at 14 and 41 days after the betamethasone injections.

The UK Multicentre Trial contributes further evidence of the effectiveness of antenatal corticosteroids in the prevention of RDS in preterm infants. Its use should be restricted to women in whom glucocorticoids are not contraindicated because of maternal disease, severe hypertension or infection, including amnionitis, and it is most appropriately administered when delivery is likely to occur between 26 and 34 weeks gestation and within 8 days of treatment.

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Meconium aspiration syndrome: a 6-year retrospective study

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Summary. The incidence and outcome of babies suffering from meconium aspiration syndrome (MAS) has been analysed in a 6-year review of 38 395 births at Guy's Hospital and Queen Charlotte's Maternity Hospital. One in 533 births (0·2%) was complicated by MAS, the mortality rate for which was 1 in 12. There was also a number of babies identified as possibly suffering from 'subclinical MAS' but no deaths occurred in this group. Males were more affected than females.

Meconium aspiration syndrome (MAS) continues to be a sporadic problem with potential for causing neonatal death. Usually the baby is otherwise healthy and mature, so compounding the disaster. Early reports of aggressive pharyngeal and endotracheal suction indicated the condition might be preventable (Ting & Brady 1975; Carson *et al.* 1976). Sadly this is not so, and in a recent communication (Hudson & Stimmler 1986) there is evidence to suggest that MAS may be on the increase. The present study analyses the incidence and outcome of MAS at two London hospitals over a 6-year period.

Patients and methods

Cases of meconium aspiration syndrome occurring at Guy's Hospital and Queen Charlotte's Maternity Hospital (QCMH) during the period 1981–1986 have been investigated by examining the medical records of all babies entering the special care baby units (SCBU). At QCMH in addition to the SCBU there is an intermediate care ward for babies who do not need any specific therapy, but because of certain risk factors are deemed to require close supervision in the early neonatal period. Grades 2 and 3 meconium staining of the amniotic fluid at delivery (O'Driscoll & Meagher 1986) is one of the indications at QCMH for admission to the intermediate care ward and so these records have also been reviewed.

Because MAS may present a similar clinical picture to transient tachypnoea of the newborn, pulmonary infection and respiratory distress syndrome, strict criteria have been adopted for labelling a baby as having suffered from meconium aspiration. The criteria were (i) the presence of meconium in the trachea at birth followed subsequently by tachypnoea but without evidence of infection (negative blood cultures); (ii) a chest radiograph showing the characteristic appearances of MAS (scattered opacities with a tendency to overexpansion of the lungs) after evidence of meconium-stained amniotic fluid but no evidence of meconium in the trachea, or subsequent pulmonary infection; and (iii) histological confirmation of meconium in the alveoli at autopsy.

In addition to those babies labelled as having MAS, there was a group suspected of having MAS, but in whom confirmation was lacking. These babies were born in the presence of meconium-stained amniotic fluid (grade 2 or 3), went on to develop tachypnoea in the absence of

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infection but had neither evidence of meconium in the trachea at birth nor a positive chest radiograph. For the purpose of discussion this group is classified as 'subclinical MAS'.

Although Guy's and QCMH are administered by different health authorities, the clinical management at delivery is similar in as much as a paediatrician attends all deliveries where the labour is associated with meconium staining of the amniotic fluid. The baby's nasal passages and oropharynx are sucked out before birth of the trunk, usually by a midwife, and on completion of the second stage the baby is handed to the paediatrician for endotracheal suction under direct vision. Chest compression is not routinely employed in either unit, but at Guy's the paediatricians favour endotracheal wash-out with normal saline if thick meconium is seen below the cords.

Results

There were 38 395 babies born at Guy's Hospital and QCMH in the 6 years under review. During this time 72 were deemed to have suffered from MAS (67 had meconium in the trachea at birth, four were diagnosed on chest X-ray and one at autopsy). This gives an incidence of 1 in 533 total births (0·2%). There were a further 19 babies with possible 'subclinical MAS' when meconium was not seen in the trachea, but tachypnoea occurred subsequently.

Males were more often affected than females in both groups. The ratios were 1·8:1 in the MAS group and 2·8:1 in the 'subclinical' group. Using the binomial theorem for statistical analysis these differences were both significant ($P<0{\cdot}25$ and $<0{\cdot}5$ respectively).

Only four babies in the two groups weighed <2·5 kg, and apart from one unbooked patient whose baby weighed 2·0 kg, all pregnancies had completed 38 weeks gestation. The mean Apgar score at 5 min was 7·4 for the MAS group and 9·1 for the 'subclinical' group. These values are significantly different ($t = 0{\cdot}4$; $P<0{\cdot}001$) Of the 72 MAS babies 42 (58%) required oxygen, and of these, 23 (55%) needed ventilating. The average length of stay in SCBU (and intermediate care at QCMH) was 6·1 days for MAS babies. Six of these babies died (3 male and 3 female) giving a mortality rate of 1 in 12 (8·3%) of all cases of MAS (Table 1). There were no deaths in the 'subclinical' group, the average length of stay in SCBU was 4·9 days.

Discussion

Without endotracheal suction at birth up to 3% of babies born at term are likely to develop MAS, and one in four of them would die (Carson *et al.* 1976). Intensive neonatal resuscitation can reduce the incidence of MAS by a factor of 10 to around 0·3% of births (Davis *et al.* 1985) and this concurs with our figure of 0·2%. If only term births are considered the figure is probably nearer 0·6% (Rosegger *et al.* 1982).

The mortality rate from MAS is more difficult to assess since quoted figures vary widely. Fox *et al.* (1977) and Mitchell *et al.* (1985) reported no deaths in 35 and 9 babies respectively. Rosegger *et al.* (1982) reported two deaths in 27 babies (7·4%), similar to the recent experience of Benny *et al.* (1987) who reported four deaths in 66 babies (6·1%). In contrast to this, Davis *et al.* (1985) reported 12 deaths in 30 infants (40%). Our experience of 72 infants with MAS shows a mortality rate of 8·3% and this we feel is probably a realistic representation of the current situation.

For the most part, the babies destined to develop MAS start with a low Apgar score and meconium in the trachea. Tachypnoea with or without the characteristic chest radiograph appearances follows, to the extent that many will require ventilation. We believe, however, that there may be a second group of babies with near-normal Apgar scores and no meconium in the trachea and yet pneumonitis subsequently develops ('subclinical MAS'). That meconium may be inhaled directly into the alveoli has been shown at autopsy (Byrne & Gau 1987), making a negative diagnosis of aspiration at birth difficult to ascertain This we feel justifies the concept of an intermediate care ward where these high-risk babies may be closely observed for the first 24 h.

The baby whose head crowns without previously having inhaled meconium-stained fluid should be prevented from doing so at birth by active airway management, including endotracheal suction under direct vision. What then of the baby who inhales meconium-stained fluid during labour? This may occur, especially if the fetus becomes hypoxic (Manning *et al.* 1978). Hypoxic gasping has been shown to occur experimentally in animals (Boddy & Dawes 1975; Block *et al.* 1981). Goodlin (1970) has advocated 'sedating' the fetus *in utero* by administering narcotic drugs to the mother in cases where the amniotic fluid is heavily meconium

Table 1. Analysis of infants with meconium aspiration syndrome (MAS) at Guy's Hospital and Queen Charlotte's Maternity Hospital (QCH) during the years 1981 to 1986

		Numbers with pneumonitis		Numbers requiring oxygen		Numbers requiring ventilation		Deaths	
Year	Total deliveries	MAS confirmed	MAS not confirmed	MAS confirmed	MAS not confirmed	MAS confirmed	MAS not confirmed	MAS confirmed	MAS not confirmed
1981									
Guy's	1899	1	2	1	2	0	0	0	0
QCH	4048	0	2	0	0	0	0	0	0
1982									
Guy's	2164	2	0	1	0	1	0	0	0
QCH	3916	6	0	2	0	1	0	0	0
1983									
Guy's	2093	7	0	6	0	2	0	1	0
QCH	4182	10	0	6	0	5	0	2	0
1984									
Guy's	2285	11	0	8	0	1	0	0	0
QCH	4364	12	7	4	1	2	1	0	0
1985									
Guy's	2338	6	2	3	1	2	0	2	0
QCH	4547	6	5	2	1	1	0	0	0
1986									
Guy's	2314	4	1	4	0	4	0	0	0
QCH	4245	7	0	5	0	4	0	1	0
Total	38 395	72	19	42	5	23	1	6	0

stained. He maintains that by depressing fetal respiration during labour, hypoxic gasping is less likely to occur. Attractive as this theory is, the thought of sedating a fetus, which may be compromised already, will not appeal to many obstetricians, or so it would seem. Certainly Dooley *et al.* (1985) found no evidence that maternally administered narcotics in labour reduced the number of babies presenting at birth with meconium below the cords.

The passage of meconium *in utero* results from physiological maturity in some babies, a concept first put forward by Fenton & Steer (1962), citing work by Desmond *et al.* (1956). Certainly there would have been only a single infant with MAS in our series, as opposed to 72, had all deliveries taken place by 38 weeks. Bearing in mind the body of opinion which today supports non-intervention in childbirth, it is of paramount importance that fetal hypoxia in labour is avoided in post-term pregnancies with meconium-stained amniotic fluid, albeit not of hypoxic origin. One must question the use of oxytocic drugs in such labours, and in grades 2 and 3 especially, a strong case can be made for serial fetal blood sampling in addition to continuous fetal cardiotocography. Whether early resort to caesarean section would reduce the incidence of MAS is as yet undetermined. Possibly the time has arrived for considering a randomized trial of elective caesarean section versus labour for those patients with factors predisposing to fetal hypoxia (pre-eclampsia, antepartum haemorrhage etc.), in addition to meconium staining of the amniotic fluid before the onset of established labour.

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A longitudinal study of circulating progesterone, oestradiol, hCG and hPL during pregnancy in type 1 diabetic mothers

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Summary. Serum progesterone, oestradiol, human chorionic gonadotrophin (hCG) and human placental lactogen (hPL) were determined serially throughout 27 pregnancies in insulin-dependent diabetic patients from Newcastle (UK), 15 such patients from Stockholm (Sweden) and in 69 normal women having uncomplicated pregnancies. Mean progesterone, oestradiol and hCG concentrations were somewhat higher in the diabetic women during the third trimester but hPL values were not different from normal. The increased hormone concentrations did not relate to the increased birthweights or placental weights in the diabetic women. It is suggested that the usual physiological endocrine changes during normal pregnancy are relatively undisturbed by insulin-dependent diabetes or the degree of diabetes control achieved.

In a previous report Aspillaga *et al.* (1983) described the changes occurring in serum progesterone, oestradiol, human chorionic gonadotrophin (hCG), human placental lactogen (hPL) and prolactin throughout normal pregnancy. The study was longitudinal and the women taking part were chosen for their good general health, uncomplicated pregnancy and subsequent delivery of a live healthy child. Having described the physiological pattern and range of these endocrinological responses we wished to determine the possible influence of changes in maternal health and whether any alteration in the hormonal milieu affected infant birthweight. Diabetes mellitus offers a good model, being a disorder which affects the general health of the mother as well as the metabolic environment in which conception and fetal development occur and it is often associated with babies of increased birthweight.

There is no clear consensus about the effect of diabetes on pregnancy hormones. Progesterone levels have been reported to be similar in normal and diabetic pregnancies (Lindberg *et al.* 1974*a*) or higher in diabetic pregnancy (Klebe & Goede 1974); few data are available relating to oestradiol levels but Lindberg *et al* (1974*b*) reported circulating values within the normal range.

Reports also conflict regarding the changes in hCG levels; Aubry & Nesbit (1970) found normal levels in diabetic patients whereas Crosignani *et al.* (1974) found normal hCG levels in pregnancies with good diabetic control but abnormally high levels in severe diabetics with poor metabolic control A study of 84 pregnant patients by Selenkow *et al.* (1971) also

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showed extremely high hCG values in diabetic women when compared with normal though the degree of metabolic control was not stated.

Circulating hPL levels during diabetic pregnancy have been more widely studied and variously reported as normal (Crosignani *et al.* 1974) or high (Selenkow *et al.* 1971), particularly if pregnancy was complicated by hypoglycaemia, ketoacidosis or hydramnios (Cohen *et al.* 1973).

Although several of the above studies were longitudinal (Aubry & Nesbit 1970; Selenkow *et al.* 1971; Cohen *et al.* 1973) and some reported concentrations of more than one hormone in the same subjects (Aubry & Nesbit 1970; Selenkow *et al.* 1971) their data conflicted. We report a longitudinal study of the changes occurring in the circulating levels of progesterone, oestradiol, hCG and hPL throughout pregnancy and their relation to birthweight and placental weight in two groups of diabetic women: 25 insulin-dependent diabetics from Newcastle (UK) and 15 from Stockholm (Sweden). As a control group similar longitudinal data are reported for a group of 69 normal healthy women having uncomplicated pregnancies, which is more than double the number reported previously (Aspillaga *et al.* 1983).

Patients and methods

Newcastle group

Data were obtained from 25 insulin-dependent diabetic pregnant women; two were studied during two successive pregnancies thus giving information from 27 pregnancies. None of the patients had any medical problem other than diabetes. Each pregnancy resulted in the birth of a live healthy singleton infant. Table 1 summarizes the clinical details of the patients included in the study; the diabetic women were of similar age as the normal women, they were not obese, and still had normal blood pressures by 36 weeks gestation though one developed severe hypertension soon after; all but two were non-smokers. White classification showed a distribution of B, C and D classes in both 'well' and 'poorly' controlled groups as defined below.

In 17 of the diabetic pregnancies, delivery was after 37 completed weeks; of the 10 pregnancies delivered ≤37 weeks, six were spontaneous, two were by elective caesarean section because of severe hydramnios, one was an elective section because of the poor previous obstetric history (two unexplained stillbirths), and the patient referred to above who was delivered by emer-

Table 1. Clinical details of the normal and diabetic patients

		Diabetic	
	Normal (*n*=69)	Newcastle group (*n*=25)*	Stockholm group (*n*=15)
Age at delivery (years)			
Mean (range)	29·3 (22–39)	27·3 (20–38)	28·1 (25–39)
Previous pregnancies			
Range			
<28 weeks	0–2	0–2	0–1
≥28 weeks	0–3	0–2	0–3
Mean body mass index at 20 weeks (kg/m²)			
Mean (range)	23·8 (20·3–31·7)	25·6 (21·4–31·5)	24·4 (21·0–29·0)
Mean arterial pressure at 36 weeks (mmHg)			
Mean (range)	37 (62–107)	92 (83–107)	96 (80–120)
Gestation at delivery (completed weeks)	>37	5 at 36 5 at 37 17 after 37	3 at 36 2 at 37 10 after 37
White classification			
Well controlled	—	6B; 11C; 2D	6B; 5C; 3D; 1F
Poorly controlled	—	2B; 3C; 3D	—

* Results are given for 27 pregnancies.

Table 2. Numbers of patients contributing data throughout pregnancy

	Gestation (weeks)												
Patient group	3	4	6	8	10	12	16	20	24	28	32	36	38
Diabetic (Newcastle)													
Well controlled (n=19)	—	3	5	9	11	14	16	16	18*	18*	18*	16	8
Poorly controlled (n=8)	—	2	4	5	6	7	8	7	8	8	8	6	1
Diabetic (Stockholm) (n=15)	—	—	—	15	15	15	15	15	15	15	15	15	10
Normal (n=69)	38	27	44	63	62	69	66	66	67	66	67	67	59

* Three women failed to attend on one occasion each.

gency section because of the acute onset of severe hypertension and proteinuria. No delivery occurred before 35 weeks.

In general the diabetic patients determined their own blood glucose concentrations using BM-Test 20–800 strips (Boehringer) by sampling five times during the day: fasting and at 11.00, 15.00, 18.00 and 22.00 hours; this was undertaken at least twice-weekly. The women were seen at frequent intervals for routine antenatal observations, assessment of glucose control, and determination of HbAl using agar gel electrophoresis (Menard *et al.* 1980). The 69 normal control patients had uncomplicated past obstetric histories, ovulated spontaneously, had normal pregnancies and were delivered of live healthy singleton infants after 37 completed weeks. Blood samples for hormone assay were obtained from both diabetic and normal patients at 6, 8, 10, 12, 16, 20, 24, 28, 32, 36 and 38 weeks: due to holidays and other events not every patient was able to attend on every occasion and the actual numbers of patients attending throughout pregnancy are given in Table 2.

Stockholm group

An additional group of 15 insulin-dependent diabetic women from Stockholm contributed to the study. Their clinical details are given in Table 1. All but two were non-smokers. Three women were delivered at 36 weeks and the remainder between 37 and 41 weeks gestation; eight had a normal vaginal delivery (four spontaneous and four induced) and seven were delivered by caesarean section. The indications for the sections were progressive retinopathy (two patients), contracted pelvis (three patients) and pre-eclampsia in two patients occurring at 36 and 40 weeks gestation.

Blood glucose was monitored six times per day every day from the time pregnancy was diagnosed to delivery. This was by reagent strip but read using a reflectance meter in each case; the results have been expressed as the mean of 3-week groups. HbAlc was determined at the stages of pregnancy shown in Table 3 using the method of Jeppsson *et al.* (1980). Blood samples for hormone determinations were also obtained at 12, 20, 28 and 36 weeks of pregnancy and all of the assays were performed in Newcastle.

Assays

Sera were stored at −20°C and all samples from an individual patient were assayed together for each hormone to minimize across-assay variability. The detailed radioimmunoassay methods are documented by Aspillaga *et al.* (1983).

Statistical analyses

Methods employed were the two-sample t-test (on log-transformed data in the case of the hormones), determination of Pearson's correlation coefficient and Spearman's rank correlation test.

Results

Diabetic control

In the Newcastle group, most patients were first seen in the first trimester (Table 2) and came regularly thereafter so that each provided about 50 blood glucose profiles. We chose reasonably strict criteria for assessment: if the mean daily blood glucose level reached 10 mmol/l or if the glycosylated haemoglobin reached 10% of total haemoglobin on any two occasions during the whole of pregnancy, control was regarded as poor. On these definitions 19 pregnancies were well controlled and eight were poorly controlled. Table 3 illustrates the mean blood

Table 3. Blood glucose, HbAl and insulin requirement from 8 weeks gestation in pregnant diabetic women

		Daily plasma glucose (mmol/l)		HbAl (%)		Total daily insulin (units)	
Gestation (weeks)		Newcastle group	Stockholm group	Newcastle group	Stockholm group	Newcastle group	Stockholm group
8	A	5·0 (1·6)	8·4 (2·4)	8·6 (1·9)	9·8 (2·1)	51·1 (18·0)	—
	B	7·7 (3·1)		10·5 (1·3)		57·2 (21·2)	—
10	A	6·6 (1·1)	7·1 (1·3)	8·1 (1·4)	9·0 (2·1)	51·2 (13·9)	—
	B	6·3 (1·0)		10·1 (1·4)		57·2 (22·3)	—
12	A	5·8 (1·7)	6·4 (0·9)	8·5 (1·3)	8·8 (1·1)	45·1 (14·5)	—
	B	6·8 (2·6)		9·7 (1·1)		57·9 (13·6)	—
16	A	5·3 (2·1)	6·3 (0·9)	7·9 (1·3)	7·9 (1·0)	44·4 (13·2)	—
	B	8·0 (3·8)		9·2 (0·9)		54·1 (15·2)	—
20	A	6·2 (1·9)	6·6 (0·9)	7·6 (0·9)	7·8 (1·1)	49·3 (14·3)	44·1 (18·3)
	B	9·0 (2·9)		9·8 (1·1)		56·0 (16·7)	—
24	A	5·9 (1·5)	6·7 (0·9)	7·8 (1·1)	7·6 (1·0)	57·3 (17·0)	—
	B	7·7 (1·9)		10·7 (1·2)		64·6 (20·6)	—
28	A	6·8 (1·5)	6·7 (1·1)	7·5 (1·1)	7·3 (1·2)	64·5 (18·8)	55·9 (19·2)
	B	7·8 (2·2)		10·2 (2·5)		77·7 (18·9)	—
32	A	5·9 (1·8)	6·1 (1·2)	7·9 (1·2)	7·1 (1·4)	72·3 (19·3)	—
	B	7·0 (2·7)		10·8 (2·1)		84·9 (19·3)	—
36	A	5·1 (1·7)	6·4 (0·8)	7·9 (1·3)	6·9 (1·0)	72·9 (23·3)	63·1 (25·4)
	B	4·9 (1·5)		8·0 (0·9)		75·2 (28·3)	—
38	A	4·6 (0·7)	6·3 (0·9)	7·3 (0·8)	6·5 (1·1)	75·4 (28·3)	—
	B	—		—		—	—

A, Well controlled; B, poorly controlled.
Results are means (SD) values.

glucose values in the interval between antenatal visits for both groups. Also shown are the mean glycosylated haemoglobin values; the normal pregnancy range is 5·8–7·3%. The mean total daily insulin doses (Table 3) show that the requirements of both groups increased to the same proportional extent as pregnancy progressed; while the poorly controlled women needed more insulin the differences between the two groups were never statistically significant. The incremental changes in insulin requirements from the first trimester to term varied greatly between patients in both the well and poorly controlled groups.

In the Stockholm group, the patients were selected on the basis of being well controlled. Their glucose and HbAl values and their increased need for insulin were not found to be different from those of the Newcastle well-controlled group except at 38 weeks where Newcastle mean glucose values were lower; however, this was a function of small numbers, since only the best-controlled patients remained to be delivered at this time.

Birthweights and placental weights

Birthweights, expressed as the difference between actual birthweight and the expected birthweight calculated according to length of gestation, maternal parity, infant sex and maternal height and weight (Altman & Coles 1980), showed that the mean birthweight of the babies both in the well-controlled and in the poorly controlled Newcastle diabetic groups was significantly heavier than that in the normal group (Table 4). Only two babies from Stockholm were below the 50th centile but they affected the mean. The same was true of placental weights in the Newcastle group, but not in the Stockholm group, where two exceptionally small placentas were associated with babies of normal weight.

Hormones

Figures 1–4 illustrate the range for progesterone, oestradiol, hPL and hCG during normal pregnancy with the geometric mean values derived from the Newcastle diabetic groups (logarithmic scale). In Fig. 4 the geo-

Table 4. Means of the differences between the actual birthweight and the expected birthweight† of the babies of normal and diabetic women together with similar data for the placentas‡

Patient group	Number of patients	Mean and standard deviation of birthweight difference (g)	Mean and standard deviation of placental weight difference (g)
Normal	69	−10 (342)	8 (117)
Diabetic (Newcastle)			
Well controlled	19	613** (655)	121* (183)
Poorly controlled	8	746** (608)	142* (148)
Total	27	652** (633)	127* (171)
Diabetic (Stockholm)	15	266*** (547)	−52§ (157)

Significance of difference from mean of normal group *$P<0\cdot01$; ** $P<0\cdot001$, *** $P<0\cdot02$.

Well and poorly controlled groups not different from each other.

† Altman & Coles (1980).

‡ Thomson *et al.* (1969).

§ Two placentas of exceptionally low weight relative to infant birthweight.

metric mean values for hCG from the Stockholm group are also shown. The hormone data are summarized in Table 5.

Progesterone. Using the Newcastle diabetics as a single group the serum progesterone concentrations were significantly higher than for the normal group at 28, 32 and 36 weeks gestation ($P<0\cdot01$). When stratified according to the degree of diabetic control it was the well-controlled women who achieved higher concentrations ($P<0\cdot01$), the poorly controlled women having values similar to the normal group. However, this was not the case for the well-controlled Swedish women who did not differ from normal except at 36 weeks when progesterone concentrations were somewhat higher ($P<0\cdot05$).

Oestradiol. The serum levels in the Newcastle diabetics were higher than normal at 28, 32 and 36 weeks ($P<0\cdot001$) and even when the group was divided according to the degree of diabetes control the values remained higher than normal ($P<0\cdot01$ for both groups). The Swedish women had higher levels than normal at 36 weeks ($P<0\cdot001$).

hCG. The findings were reversed for this hormone; taking the Newcastle group as a whole the hCG values were above normal at 28 and 32 weeks ($P<0\cdot01$) but due to the poorly controlled women ($P<0\cdot001$) since the well-controlled did not differ from the normal group. On the other hand, the well-controlled Swedish women had significantly raised values at 20, 28 and 36 weeks ($P<0\cdot01$) but these were not different from those in the poorly controlled Newcastle women.

hPL. The levels of this hormone did not differ from normal in either the Newcastle women, however grouped, or the Stockholm women.

Relations between hormones, birthweights and placental weights

Although the well-controlled patients in Newcastle had higher than normal progesterone

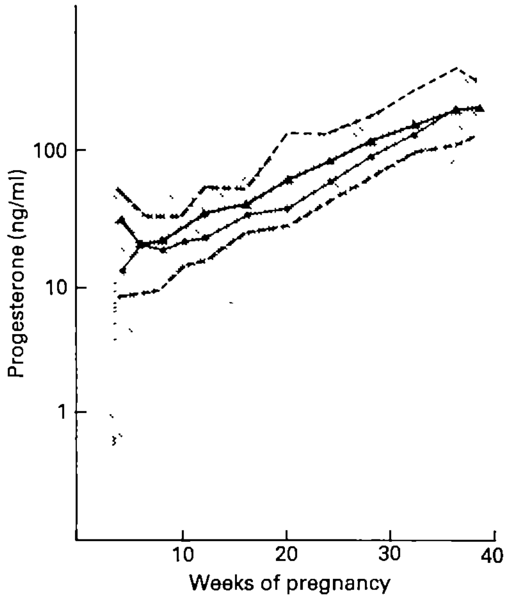

Fig. 1. Mean and range for serum progesterone concentration in diabetic patients throughout pregnancy. Stippled area indicates normal range. ▲, Well controlled; ●, poorly controlled.

Table 5. Serum progesterone, oestradiol and hCG in the third trimester

Patient group	Gestation (weeks)	Progesterone (ng/ml)		Oestradiol (pg/ml)		hCG (U/ml)	
		Mean	Log mean (SD)	Mean	Log mean (SD)	Mean	Log mean (SD)
Normal	28	85·7	1·93 (0·19)	13 552	4·08 (0·20)	11·97	1·08 (0·31)
	32	113·2	2·05 (0·18)	17 418	4·24 (0·19)	13·93	1·14 (0·33)
	36	143·2	2·16 (0·20)	20 941	4·32 (0·17)	17·99	1·26 (0·35)
Diabetic (Newcastle)	28	112·2**	2·05 (0·11)	19 055***	4·28 (0·16)	20·89**	1·32 (0·38)
	32	151·4**	2·18 (0·13)	22 909***	4·36 (0·17)	25·70**	1·41 (0·41)
	36	204·2**	2·31 (0·12)	28 184***	4·45 (0·17)	26·30	1·42 (0·36)
Diabetic (Stockholm)	28	102·3	2·01 (0·13)	13 490	4·13 (0·12)	43·70**	1·64 (0·33)
	32	—	—	—	—	—	—
	36	190·5*	2·28 (0·09)	26 915***	4·43 (0·16)	53·70**	1·73 (0·32)

Significantly different from normal: * $P<0{\cdot}05$; ** $P<0{\cdot}01$; *** $P<0{\cdot}001$.
Results are geometric mean and log mean (SD) values.

levels in the third trimester and the poorly controlled patients had higher than normal hCG levels during this time, it did not follow that within this diabetic group as a whole the poorly controlled patients provided all the low progesterone concentrations or that the well-controlled patients provided the low hCG concentrations. On ranking the progesterone and hCG values at 28 and 36 weeks, the lowest progesterone values did not appear to correlate with the highest hCG ($r=0{\cdot}3$) concentrations. However, in the normal group, progesterone and hCG values did show a significant correlation ($r=0{\cdot}4$, $P<0{\cdot}001$) at 36 weeks.

Despite the lack of any change in circulating hPL concentrations in diabetic compared with normal women some interesting correlations emerged during the third trimester. Considering all the Newcastle patients as one group, hPL correlated significantly with progesterone levels at 32 and 36 weeks ($r=0{\cdot}6$, $P<0{\cdot}01$; Spearman). This persisted when they were divided into well-controlled and poorly controlled groups ($r=0{\cdot}8$, $P<0{\cdot}01$; $r=0{\cdot}9$, $P<0{\cdot}01$ respectively). In the well-controlled group, hPL also correlated with hCG at 28 and 32 weeks ($r=0{\cdot}6$, $P<0{\cdot}01$). Partial correlations eliminating the effect of time confirmed these hormonal pair correlations from 28 to 36 weeks for diabetic women but no such correlations were found in the normal pregnant women ($r=-0{\cdot}1$, $r=0{\cdot}3$ respectively).

To determine whether the circulating hormone levels were reflecting placental mass or birthweights, the concentration of each hormone at 32 and 36 weeks gestation was correlated with placental weight and birthweight after these had been corrected for maternal parity, stature, infant sex and length of gestation; no significant correlations with $P<0{\cdot}01$ were found in the diabetic groups as a whole or when subdivided according to control, although the correlation between hPL at 32 weeks (when most patients attended) and corrected birthweight was 0·48 ($P<0{\cdot}02$). In our normal group of 69 women there was a correlation between serum hPL concentration and corrected placental weight ($r=0{\cdot}3$, $P<0{\cdot}01$) but not between hPL and birthweight ($r=0{\cdot}1$).

Change in insulin requirements

No significant correlations ($r<0{\cdot}2$) were found between hPL or any of the other hormones and

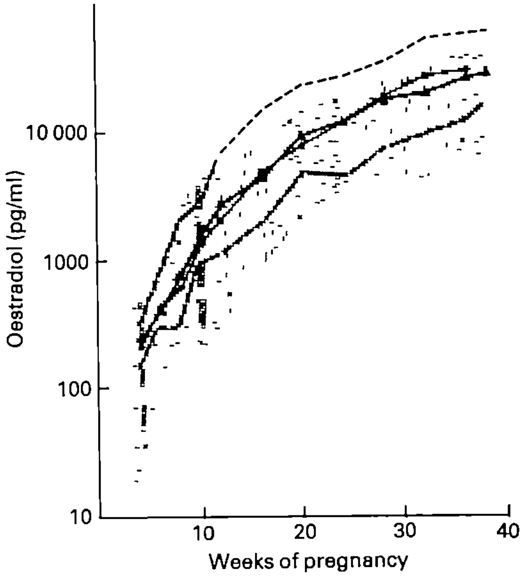

Fig. 2. Mean and range for serum oestradiol concentrations in diabetic patients throughout pregnancy Stippled area indicates normal range. ▲, Well controlled; ●, poorly controlled.

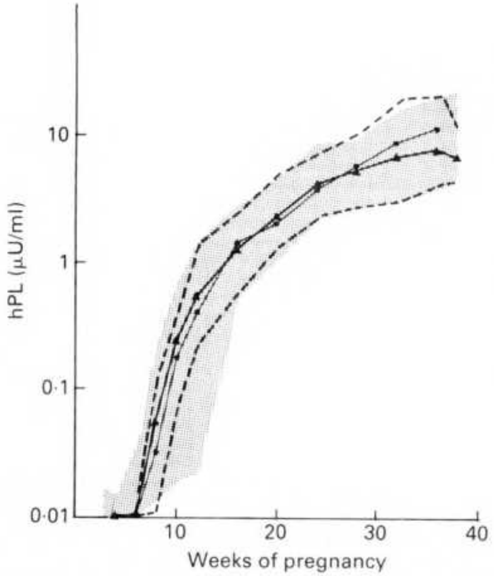

Fig. 3. Mean and range for serum hPL concentrations in diabetic patients throughout pregnancy. Stippled area indicates normal range. ▲, Well controlled; ●, poorly controlled.

the increase in insulin requirements which most insulin-dependent diabetics needed later in pregnancy.

Discussion

The term diabetes mellitus describes a disorder of metabolism but not the clinical status of an individual. Amongst insulin-requiring patients there will be variability dependent upon the age at onset of the illness, its duration, the type of regimen followed, the presence of large and small vessel disease and associated factors such as cigarette smoking and hypertension as well as ethnic and social factors. Although various classification systems have been suggested to take account of these variables, none has received universal acceptance. The same constraints apply to the management of the condition: any definition of 'well-controlled' and 'poorly controlled' diabetes is necessarily arbitrary because there are no generally agreed criteria upon which to base a clinical opinion. As pregnancy is 9 months long the control status of a patient can change from being poorly controlled when she first attends the antenatal clinic to well controlled when patient compliance and co-operation have been achieved. Finally the number of observations of blood glucose concentrations made by individual patients influences our views; a well-controlled patient who offers daily measurements has more chance of being told she occasionally has 'bad' days than the woman who offers fewer data but all of them apparently 'good'.

We have attempted to allow for some of these variables by defining our criteria for well-controlled and poorly controlled women in Newcastle and also studying a group of pregnant women from a different country but with a similar standard of living and way of life who achieved good control judged by more frequent blood-glucose monitoring. Some endocrine differences were noted: serum progesterone and oestradiol levels during the last trimester of diabetic pregnancies were somewhat higher on average than in normal women but this was more apparent in Newcastle than Stockholm. Circulating hCG levels were also higher in diabetic women but this appeared to be in the poorly controlled women in Newcastle and the well-controlled Swedish women. In normal pregnancy, hPL is related to placental size (Aspillaga

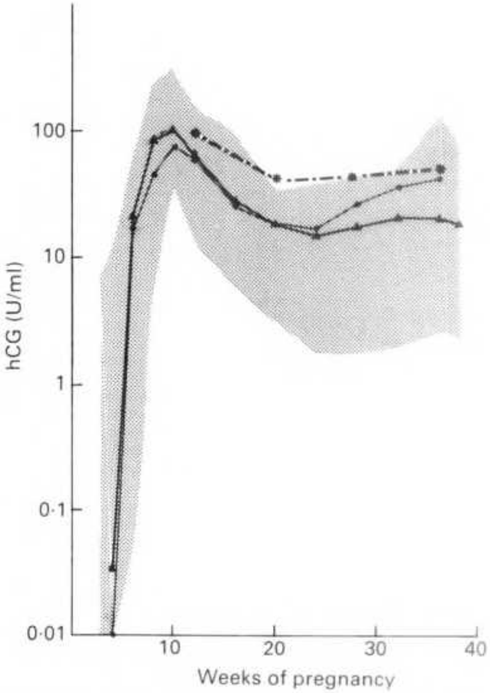

Fig. 4. Mean serum hCG concentrations in Newcastle and Stockholm diabetic patients throughout pregnancy. Stippled area indicates normal range. ▲, Well controlled (Newcastle diabetics); ●, poorly controlled (Newcastle diabetics); *, Stockholm diabetics.

et al. 1983). As placental weight is usually increased in diabetic pregnancies it might have been assumed that this would cause an increase in circulating hPL and that the relation between the placenta and hPL would remain. Such is not the case and no relation was found between hPL and placental weight in these diabetic women. It has been suggested that hPL may be a stimulator of IGF-I (growth factor) since women who fail to produce hPL have decreased IGF-I levels (Parks *et al.* 1985). As IGF-I correlates with birthweight in both diabetic and normal women (Hall *et al.* 1986), this would create a link between hPL and fetal growth. But despite the fact that the average birthweight of all the babies of the diabetic women described here was 514 g above the normal mean birthweight, hPL values were the same as in normal women and did not correlate with birthweight.

It has been suggested that hPL and progesterone are involved in the decreased tolerance to glucose which usually occurs in the second half of normal pregnancy (Kalkhoff *et al.* 1970; Laube *et al.* 1972; Sutter-Dub *et al.* 1973; Green *et al.* 1978), possibly due to alterations of the insulin receptors (Beck-Nielsen *et al.* 1979). However, insulin-binding capacity is not diminished in the pregnant diabetic (Pedersen *et al.* 1981) in spite of generally enhanced hormone levels and so again there seems to be little direct connection between altered hormone levels and diabetic pathology.

For some years it was generally thought that the increased birthweight of babies born to insulin-dependent diabetic women was caused by poor control, reflected in hyperglycaemia. Indeed, it was held that big babies were evidence of poor maternal control and that macrosomia would disappear with better patient education. Such is not the case and several reports have indicated that macrosomia can occur in the most rigorously controlled women (e.g. Russell *et al.* 1984; Knight *et al.* 1983). In the well-controlled Newcastle women and the women from Stockholm the mean infant birthweight was still 514 g heavier than average allowing for maternal parity and infant sex. This suggests that while hyperglycaemia may be one factor influencing birthweight, diabetes causes a wide range of metabolic disturbances some of which may influence fetal growth even when hyperglycaemia is avoided.

Our findings suggest that diabetes mellitus during pregnancy does not affect the endocrine milieu of pregnancy to any marked extent; most of the insulin-dependent diabetic women had progesterone, oestradiol, hPL and hCG responses inside the normal pregnancy range. Infant and placental weight are usually above average, irrespective of the degree of glycaemic control achieved, but neither weight is correlated with the changes in hormone concentration. Finally the increased need for insulin displayed by most women during the last trimester does not relate to these endocrine changes or infant birthweight. It is suggested therefore that the hormone response of diabetic women is similar to that of normal women throughout pregnancy, and other explanations for the increase in birthweight and insulin needs will have to be sought.

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Plasma secretin concentrations during normal human pregnancy, delivery, and postpartum

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Summary. Plasma concentrations of secretin were measured at 4-week intervals throughout eight normal pregnancies and again twice postpartum, and in another six women during parturition and the early postpartum period. Comparisons were made with levels in 16 normal non-pregnant women. Plasma secretin concentrations increased during pregnancy with maximum levels at 36 weeks. The increase was statistically significant from week 28 to 36, compared with non-pregnant levels. By 5 days after delivery plasma secretin levels were similar to the non-pregnant levels. No significant changes in plasma secretin were observed during delivery and early postpartum. The altered secretin levels may be of importance for heartburn in pregnancy, calcium metabolism, and the changes in renal haemodynamics.

Secretin, a basic polypeptide consisting of 27 amino acids, was the first hormone ever characterized (Bayliss & Starling 1902). So far, the only well-defined mechanism for its release into plasma is acidification of the upper small intestine. The major physiological action of secretin is the stimulation of bicarbonate secretion into the duodenum. Several other actions of secretin have also been described, including inhibition of the lower oesophageal sphincter pressure (Rayford *et al.* 1976), increase in plasma levels of parathyroid hormone and calcitonin (Sethi *et al.* 1983), increase in renal blood flow and glomerular filtration rate (Becker *et al.* 1982; Marchand *et al.* 1972), and increase in cardiac output (Gunnes *et al* 1983). Since these physiological changes are characteristic of pregnancy, and we have recently described substantially elevated plasma secretin concentrations in late pregnancy (Jenssen *et al.* 1988), there may be, in part, a causal link. The pattern of change in plasma secretin during pregnancy has not been determined, and the present longitudinal study was undertaken to measure plasma secretin levels throughout normal human pregnancy. In addition, we determined the plasma secretin concentrations during delivery and postpartum.

Patients and methods

Eight healthy women, six of them primigravidae, mean age 31 (range 24–38) participated in the study after giving informed consent. None had pre-existing gastrointestinal disease, and all completed an uncomplicated pregnancy with delivery of full-term and healthy singleton babies of appropriate weight. The gestational age had been determined accurately by ultrasound examination. None had taken any drugs, apart from iron and folic acid supplements, for at least 3 months before pregnancy.

Blood samples were obtained as described previously (Holst *et al.* 1986*a*) every 4 weeks after 7 weeks gestation, i.e. in weeks 8, 12, 16,

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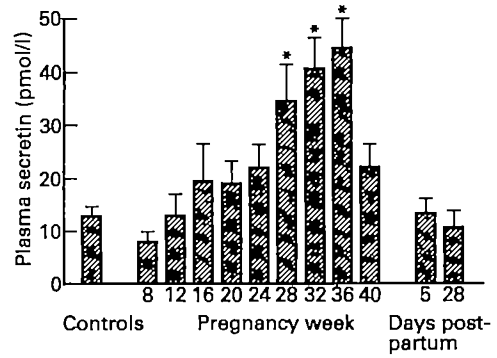

Fig. 1. Plasma secretin levels in 16 non-pregnant control women and in eight women during pregnancy and postpartum (mean ± SEM). *Significant (P<0·01) difference from the values in non-pregnant controls.

20, 24, 28, 32, 36 and 40. Additionally, two blood samples were obtained postpartum; on the fifth day after delivery and 4 weeks postpartum. On each occasion two blood samples were drawn with a 10-min interval. Plasma secretin was determined as the mean of the secretin immunoreactivity in these two samples. All blood samples were taken after an overnight fast.

Plasma from earlier studies in six pregnant women (Jenssen *et al.* 1986; Holst *et al.* 1986*b*) were also analysed to determine the levels of secretin during delivery and the early postpartum period. In this study, fasting blood samples were drawn at approximately 10, 5 and 0 min before delivery; and at 5, 15, 30, 60 and 120 min after delivery. In addition, blood samples were taken 2–3 weeks before, and 24 h as well as 1 year postpartum.

Sixteen normal, non-pregnant female volunteers, mean age 29·7 years (range 22–38), served as controls. Blood samples were obtained as described for the pregnant women. None of the controls had taken any medication for at least 3 months before the study.

Plasma secretin was measured by a radioimmunoassay method described previously (Burhol & Waldum 1978).

Statistical analyses

Statistical analyses were performed by one-way analysis of variance and multiple range analysis. P<0·05 was considered statistically significant.

Results

The results are presented in Figs 1 and 2. Plasma secretin concentrations increased throughout pregnancy, with a peak value (mean 44·5, SEM 5·5 pmol/l) at 36 weeks gestation (Fig. 1). Compared with the values in the non-pregnant control group, plasma secretin levels between 28 and 36 weeks gestation were significantly increased (P<0·01), but levels had decreased by day 5 after delivery, when they were similar to those in the control subjects.

Plasma secretin levels during delivery and the early postpartum period are shown in Fig. 2 for six individual women. Fasting plasma secretin concentrations 2–3 weeks before term showed a skewed distribution and ranged from 50 to 800 pmol/l. In two women (A and B) considerable fluctuations were seen. At, and immediately after, delivery plasma secretin levels tended to increase in all subjects, although the increase was not statistically significant.

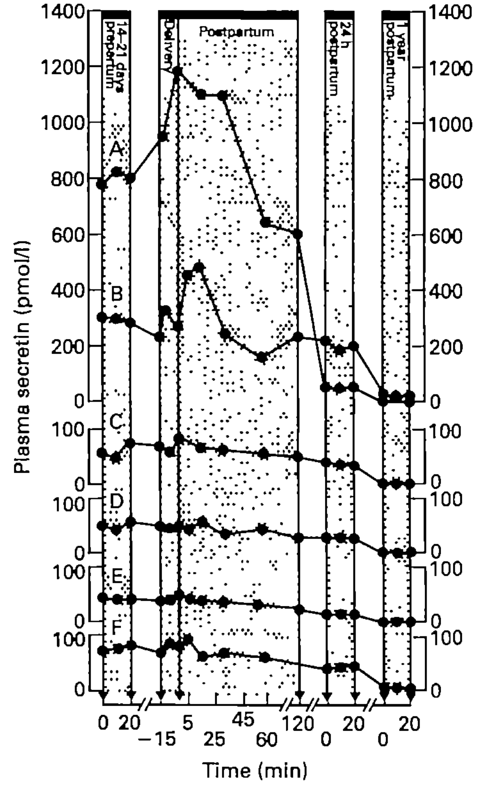

Fig. 2. Plasma secretin levels (pmol/l) in six individual women (A–F) before, during and after parturition

Discussion

This study shows that plasma secretin concentrations increase gradually during normal pregnancy in women, apparently reaching a maximum at 36 weeks gestation, and decreasing to normal, non-pregnant levels by day 5 after delivery. No significant changes in plasma secretin levels were observed during delivery and early postpartum. Our findings differ from those of McKiernan & King (1980), who found that plasma secretin concentrations were unchanged in late pregnancy and increased in the immediate hours postpartum. However, they did not state whether plasma was extracted before radioimmunoassay, a procedure precluding the detection of secretin bound to larger plasma components. Moreover, their blood samples were taken without regard to fasting, which is a prerequisite for monitoring gastrointestinal hormones.

We have recently reported on the characterization of secretin-like immunoreactivity in late pregnancy (Jenssen *et al.* 1988); we found that secretin binds to plasma protein(s) with enhanced avidity in pregnancy. Since pregnancy is known to increase the production of various binding proteins (Laurell & Rannevik 1979), the observed increase in plasma secretin concentrations during pregnancy may mainly be ascribed to an increase of one or several secretin-binding proteins.

Chromatographic studies have revealed that secretin-like immunoreactivity in unextracted plasma elutes in a peak close to albumin (Jenssen *et al.* 1988). However, it is not likely that albumin serves as a secretin-binding protein, since the concentration of serum albumin is lowered in pregnancy (Studd 1975) and its binding capacity accordingly tends to fall (Yoshikawa *et al.* 1984). So far, the presence of a secretin-binding protein must be regarded as a postulate until it is further characterized.

An increased release of secretin during pregnancy must also be considered. In the non-pregnant state the major source of secretin in the peripheral circulation is the duodenum, and the only well-defined mechanism for its release into plasma is acidification of the upper small intestine (Greenberg 1982). Pregnancy is associated with a decrease in acid secretion in early or mid-pregnancy followed by a late increase (Hytten 1980). Also, gastric tone and motility are reduced in pregnancy (Hytten 1980). Therefore, it seems unlikely that increased acidification of the duodenum can play a major role for the elevation of plasma secretin in pregnancy; more likely, the uterus or conceptional products may be the source of the elevated plasma secretin. The finding by Rogers *et al.* (1975) of plasma cord levels of secretin being approximately seven times as high as maternal plasma secretin levels at delivery supports this view. We are now investigating this possibility.

The major action of secretin, and the only one reported to be of physiological significance, is the stimulation of bicarbonate secretion into the duodenum, i.e. stimulation of alkaline pancreatic and biliary juice (Greenberg 1982), but this seems to be less important in pregnancy. It has been shown that pancreatic secretion is significantly decreased in human pregnancy (Zastrow 1975), and there is also evidence for a lowered production of bile (Holtermüller & Weis 1980). A reduction in the pancreatic and biliary response to secretin may possibly be ascribed to an increased binding of secretin to plasma proteins, causing a pre-receptor inhibition of the secretin actions. Moreover, this possible inhibition of hormonal action caused by binding proteins may be organ specific depending on the blood flow in the particular organ (Pardridge 1981).

Heartburn is a common complaint in pregnancy, and is at least partly caused by decreased distal oesophageal sphincter pressure (Hytten 1980). A diminution in lower oesophageal sphincter pressure has been demonstrated in the third trimester of pregnancy (Van Thiel *et al.* 1977), thus coinciding with the significant increase in plasma secretin levels observed in this study. Since secretin has been found to reduce the sphincter tone (Rayford *et al.* 1976), it may play a role in heartburn in pregnancy.

Pregnancy is associated with an increase in the plasma concentrations of both parathyroid hormone and calcitonin (Reeve 1980), but both these changes cannot be explained by the same stimulus of a change in plasma calcium levels. The work of Sethi *et al.* (1983) offers a possible explanation. They found that secretin infused in physiological doses caused an increase in serum parathyroid hormone and calcitonin in man, whereas serum calcium concentrations remained unchanged. Thus, the increase in plasma secretin levels during pregnancy may modulate calcium metabolism in pregnant women by increasing plasma concentrations of parathyroid hormone and calcitonin.

Pregnancy is also associated with an increase in glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) (Davison 1980). Secretin has been found to increase both GFR and ERPF in a dose-dependent manner (Marchand *et al.* 1972). Thus, secretin, among other substances, may mediate the altered renal haemodynamics observed in pregnancy.

Secretin has cardiovascular effects similar to those observed in pregnancy, i.e. increased cardiac output and blood flow to various organs (Gunnes *et al.* 1983; Becker *et al.* 1982). These effects of secretin must, however, be regarded as pharmacological. Furthermore, the cardiovascular changes in pregnancy occur within the first 10 weeks (de Swiet 1980), so that secretin can hardly be responsible.

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Pregnancy outcome after unwinding of twisted ischaemic-haemorrhagic adnexa

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Summary. Six women who became pregnant after human menopausal gonadotrophin/human chorionic gonadotrophin (hMG/hCG) treatment regimens were operated on between 6 and 21 weeks gestation with an intra-operative diagnosis of twisted ischaemic-haemorrhagic adnexa. During operation unwinding of the adnexa was performed in all patients. Monitoring of the pregnancy before and after operation by ultrasonography was normal. The postoperative period and the rest of the pregnancy were uneventful. Three women were delivered normally at term. One patient was delivered by caesarean section because of twin pregnancy with malpresentation, and two pregnancies are still ongoing beyond the first trimester. This preliminary study suggests that detorsion of ischaemic-haemorrhagic adnexa during pregnancy is an option that is not associated with subsequent complications. This approach might be adopted relatively safely when preservation of future fertility is a goal.

Torsion of the ovaries or adnexa is an uncommon complication with serious sequelae on future reproductive life.

The delay in diagnosis is due to the inconsistency and lack of impressive signs and symptoms. When diagnosis is delayed, the adnexa become congested, ischaemic, haemorrhagic and necrotic. Oophorectomy or salpingo-oophorectomy is usually performed (Hibbard 1985; Nichols & Julian 1985). In contrast, early diagnosis allows salvage by unwinding. Although torsion of the normal adnexa has been described (Berger & Robbins 1961; Chambers *et al.* 1979), this surgical emergency is more often associated with ovarian cysts, which may be the cause of this problem.

Ovarian hyperstimulation syndrome is a relatively common complication of induction of ovulation with gonadotrophins, and is more common when pregnancy results (Hack *et al.* 1970). This syndrome mainly involves bilateral enlarged ovaries with multiple cysts, which can be complicated by torsion (Schenkar & Weinstein 1978). Since the potential fertility of these infertile women should be preserved, in the last few years we have adopted a conservative management of unwinding the twisted adnexa, regardless of their appearance. We report here our preliminary experience with the procedure of unwinding the ischaemic-haemorrhagic adnexa during pregnancy.

Patients and methods

During the last 7 years, ending March 1988, we treated six patients who conceived after

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gonadotrophin therapy and had ovarian hyperstimulation syndrome complicated by adnexal torsion. Human menopausal gonadotrophin (hMG) was administered according to the individualized adjusted daily dose. Ovarian hyperstimulation syndrome was classified as described by Lunenfeld & Insler (1974). A pre-operative diagnosis of adnexal torsion was made clinically and confirmed by ultrasonography using a mechanical sector scanner (Diasonics, 3·5-MHZ Milpitas Cal). Findings consistent with the diagnosis of twisted adnexa, as described by Graif *et al.* (1984), were noted. Clinical and laboratory data were recorded in the acute stage and during the course of the pregnancy. Ultrasonographic examination was continued in three patients after delivery to establish whether follicular growth occurred in the affected ovaries.

Results

Table 1 summarizes the clinical features of the six women. Their mean age was 28 years (range 25–33). The main symptom was acute lower abdominal pain, with a palpable pelvic mass confirmed by ultrasonography. The presumed diagnosis before surgery was torsion of hyperstimulated adnexa in all six women. Laboratory findings showed leucocytosis in five patients and a slight fall in haemoglobin concentration in four patients. At laparotomy the size of the twisted ovaries ranged from 9 to 20 cm and they were twisted two to three times around their pedicle. In all patients the other ovary was enlarged but looked normal.

In all patients the twisted ovary was unwound. In two women a ruptured cyst was seen and a small wedge resection and suture of the ovary was performed. The recovery of the adnexa was watched for about 15 min before the abdomen was closed. The colour of the adnexa was somewhat changed to pink but no change in the volume or disappearance of the black foci was seen. Pathological examination of the two wedge resections showed ischaemic-haemorrhage tissue with foci of infarcts.

The time lag between onset of symptoms and surgery ranged between 28 and 154 h. The postoperative period was uneventful in all patients and the symptoms disappeared rapidly. All six women were discharged after 7 days in hospital. Follow-up with ultrasound during the pregnancy showed the ovaries to reduce in size and there was no recurrence of the symptoms. Three patients had normal vaginal deliveries at term and one had a caesarean section because of twin pregnancy complicated by malpresentation. During the caesarean section the affected ovary looked normal. The other two pregnancies are continuing normally beyond the first trimester.

Discussion

Information on adnexal torsion during pregnancy consists of a few publications, mainly case reports (Chambers *et al.* 1979; Hurwitz *et al.* 1983; Haskins & Shull 1986). Hurwitz *et al.* (1983) described early diagnosis of torsion during pregnancy in a woman with ovarian hyperstimulation but with normal-appearing non-ischaemic adnexa. The adnexal torsion was treated by unwinding with no deleterious effect on the course of the pregnancy. When the diagnosis is made early, unwinding of the twisted adnexa is the obvious choice. However, when diagnosis is delayed and the adnexa become ischaemic and look dark with foci of haemorrhagia, most surgeons perform oophorectomy or

Table 1. Clinical and laboratory features of the patients

			Twisted adnexa			Hours			
Patient no.	Age (years)	Gestation (weeks)	Side	Size (cm)	Times	Symptoms to admission	Admission to operation	Hb(g/dl)*	White blood cells × 10^2
1	29	8	Right	15	2	24	7	13·4– 8·4	205
2	28	7	Left	20	2	24	20	13·0– 9·4	140
3	28	21	Left	9	2	80	72	12·4–10·9	118
4	25	7	Left	20	3	20	8	13·0–11·0	250
5	25	13	Right	10	2	48	18	13·0–12·5	200
6	33	6	Left	15	2	150	4	13·4–12·9	136

* Change in haemoglobin concentration before operation.

salpingo-oophorectomy (Hibbard 1985; Chambers *et al.* 1979). Since torsion of adnexa occurs during the reproductive years when preservation of future fertility is important, in recent years we have adopted conservative management of the ischaemic twisted adnexa, namely unwinding of the ovary, regardless of the morphological appearance of the adnexa and the time lapse to operation. This approach in our six pregnant patients was without postoperative complications and is encouraging. To the best of our knowledge, there are no previous reports on detorsion of ischaemic adnexa in the literature.

In the one woman delivered by caesarean section the ovary was seen to be macroscopically normal. The three women examined ultrasonographically after birth were shown to have growing follicles in the affected ovary. These data suggest that ovaries which macroscopically appear to be ischaemic and even necrotic are capable of recovering and being functional.

It is of interest that all our patients were pregnant as a result of gonadotrophin treatment and had ovarian hyperstimulation syndrome. This reflects the higher frequency of adnexal torsion in association with this syndrome (Hibbard 1985).

Most surgeons have been reluctant to unwind an ischaemic ovary due to the fear of thromboembolic phenomena (Hibbard 1985; Nichols & Julian 1985). Pre-existing sluggish circulation and hypercoagulability associated with pregnancy are possible contributing factors to intravascular thrombi formation. However, this fear was not supported by Hibbard (1985) who noted no such complication in 23 pregnant women with adnexal torsion. Berger & Robbins (1961) described ovarian detorsion with severe congestion of the tube, but, although they noted a slight recovery of the ovary immediately after unwinding, they performed salpingo-oophorectomy. Our results confirm these findings and further suggest that unwinding might be the procedure of choice when preservation of fertility potential is desired.

Chambers *et al.* (1979) noted that the right ovary was more frequently prone to torsion, but this was not confirmed by Berger & Robbins (1961) who found an equal frequency of adnexal torsion in the two sides. In our study, the left side was more often affected than the right side. These conflicting data are due to small sample size, and we suggest that both ovaries have a similar risk of torsion.

In summary, from these preliminary data it seems that unwinding of ischaemic twisted adnexa is an option in patients desiring future childbearing. This procedure was not associated with any complication and did not affect the course of pregnancy. The adnexa seem to have the ability to recover not only morphologically but also functionally as reflected by follicular growth.

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The prevalence of pleural effusions in pre-eclampsia: an ultrasound study

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Summary. A prospective ultrasound study was undertaken to investigate the prevalence of pleural effusion in patients with moderate or severe pre-eclampsia. The costophrenic angles of 34 consecutive patients were scanned postpartum with a real-time sector scanner. Six patients had pleural effusions. These patients did not have a greater degree of hypertension or proteinuria than the group without pleural effusion but had early severe disease requiring early delivery. The prematurity of these infants resulted in tenfold increase in perinatal death.

In a prospective ultrasound study, Udeshi *et al.* (1988) investigated the prevalence of pleural effusion in the early postpartum period and suggested that pleural effusions are uncommon in asymptomatic mothers. This is at variance with previous work by Hughson *et al.* (1982) who retrospectively identified pleural effusions in 46% of 112 women who had had chest radiography in the immediate postpartum period. They subsequently conducted a prospective study of 30 postpartum patients and 30 healthy non-pregnant women. A 'small effusion' (blunting of the costophrenic angle) was found in 63% of the study population and 10% of the controls. One of the patients had a 'moderate effusion' (a well-rounded meniscus extending up the chest wall). Lateral decubitus films, taken in 10 postpartum patients, showed free fluid in seven.

Ultrasound has been shown previously to be better at distinguishing the nature of pleural shadows than radiology, and is able to detect volumes as small as 5 ml (Doust *et al.* 1975; Gryminksi *et al.* 1976; Lipscomb *et al.* 1981).

Udeshi *et al.* (1988) investigated 50 patients with ultrasound between 1 and 45 h after delivery and found only one patient with pleural effusions. This patient was delivered because of fulminating pre-eclampsia at 28 weeks, and chest radiography showed interstitial pulmonary oedema.

In view of these findings, we set out to investigate the prevalence of pleural effusion in women with moderate or severe pre-eclampsia and to determine whether the presence of pleural effusions was of any prognostic significance.

Subjects and methods

All women with moderate or severe pre-eclampsia delivered at the Birmingham Maternity Hospital from March 1987 to December 1987 underwent ultrasound scan of their chest on at least one occasion in the immediate postpartum period. The timing of the scan depended mainly on the time of the delivery (scans were generally performed first thing in the morning of the next working day or in the afternoon of the same day as appropriate).

Pre-eclampsia was classified according to criteria suggested by Davey & MacGillivray (1986). Moderate pre-eclampsia was defined as a diastolic blood pressure of 100 mmHg and two pluses of protein on ward testing (albustix) on two occasions. Severe pre-eclampsia was

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Table 1. Clinical details of pre-eclamptic women with and without pleural effusions

	Effusions		No effusions	
No. of patients	9		25	
Age (years)	26·3	(5·7)	27·8	(6·9)
Proteinuria (g/24 h urine)	3·2	(1·2)	3	(1·1)
Lowest albumin (mg/l)	19	(3)	21	(3·4)
Highest BP (mmHg)				
Diastolic	107	(16·4)	112	(10·2)
Systolic	157	(22·2)	164	(17·8)
Colloid given (units of 400 ml)	2·33	(2·3)	1·4	(2·2)
Crystal i.v fluids in the first 24 h (ml)	2133	(980)	2284	(950)
Gestation at delivery (weeks)	29·6	(4·4)	33·9	(4·1)*
Eclamptic fits	0		3	(12%)
Intrauterine transfer	7	(78%)	6	(24%)
Outcome†				
Intrauterine death	1	(10%)	0	
Neonatal death	3	(30%)	1	(4%)
Alive and well	6	(60%)	24	(96%)

The results show mean (SD) or *n* (%) values as appropriate.

* There were no significant differences between the two groups except for gestational age at delivery $P<0{\cdot}02$ (Student's *t*-test).

† There was one set of twins born in the group with pleural effusions.

defined as a diastolic blood pressure of ≥120 mmHg on one occasion or 110 mmHg on two occasions 4 h or more apart associated with proteinuria of ≥3 g in one 24-h urine collection.

All scans were performed with a 5-MHz electronic sector probe with an IGE RT 3000 real-time machine; all the women were scanned in bed at an angle of 45° to the horizontal if possible and in the supine or decubitus position if heavily sedated or ventilated. Longitudinal scans were obtained of both costophrenic angles.

Subsequently clinical notes and fluid balance charts were examined to obtain relevant clinical information including type and volume of fluid administered, serum albumin, urinary protein loss, blood pressure and drug therapy. If a chest radiograph was available it was also reviewed.

The results were analysed using Student's *t*-test where appropriate (Swinscow 1978).

Results

A total of 34 patients aged between 16 and 44 years (mean 27·4) were examined over the 9-month period of study. Nine (26·5%) patients were identified as having pleural effusions. There were no statistically significant differences between the nine patients with pleural effusions and the larger group of 25 patients without effusions in age (mean 26·3, SD 5·7 years and mean 27·8, SD 6·9 years, respectively) or in the delay between delivery and ultrasound scan (mean 19·3, SD 26 h and mean 20, SD 12·8 h, respectively). The mode of delivery was similar in both groups, 6 (66%) of those with effusions and 18 (72%) of those without effusions were delivered by emergency lower-segment caesarean section under general anaesthesia, one patient with an effusion (11%) and three of those without effusions (12%) were delivered by elective section with an epidural. One patient in each group had an elective caesarean section under general anaesthesia and one woman with effusions and three without were delivered vaginally.

Table 1 shows that there were no statistically significant differences between the two groups when the amount of proteinuria, measured by Dipstick, the lowest measured serum albumin and blood pressure readings were compared. The group without pleural effusions had a mean highest diastolic pressure of 112 (SD 10·2) mmHg and a mean highest systolic of 164 (SD 17·8) mmHg compared with 107 (SD 16·4) and 157 (SD 22·2) mmHg in the group with effusions. The total volume of plasma, the plasma protein fraction and intravenous crystalline fluids, in the form of 0·9% saline or Hartmann's solution in the first 24 h, were also comparable between the two groups

Some differences were found between the two groups. The mean gestational age at delivery was significantly shorter by some 3 weeks in the group with effusions. None of the women with pleural effusions developed eclamptic fits whereas three of the 25 women without effusions had fits. Furthermore, seven of the women with effusions were referred from other centres (78%), compared with only six of the women without effusions (24%).

A slightly larger percentage of patients with pleural effusions had chest radiographs (56% compared to 44%). The usual reason for the request was to check the position of a central venous pressure line. Pulmonary oedema was noted in two patients in each group.

Outcome differed significantly between the two groups in that the perinatal mortality rate was 10 times higher in the group with pleural effusions. Of the 10 babies born in this group one was stillborn and three died in the neonatal period (40%) compared with a single neonatal death (4%) in the other group.

The intrauterine death occurred in a 17-year-old girl who presented in labour at 29 weeks by dates, having concealed the pregnancy. The female infant was stillborn vaginally and weighed 1·45 kg. An autopsy was refused but the placenta was compatible with severe pre-eclampsia. Two of the three neonatal deaths were born at 27 weeks gestation with birthweights of 740 and 680 g; both babies survived only a few days. The third neonatal death in the group with pleural effusions was the second twin born at 27·5 weeks; the baby weighed 820 g and died at 92 h. The single neonatal death in the group without pleural effusions occurred in a 37-year-old woman, parity 4, whose first pregnancy had resulted in a neonatal death at 28 weeks. On this occasion she developed eclamptic fits at 27 weeks before giving birth to a 840-g infant who died at 5 days. The four neonatal deaths were born at a mean gestation of 27·3 weeks and had a mean birthweight of 770 g.

Discussion

Previous work from our department (Udeshi *et al.* 1988) showed that clinically well women did not have pleural effusions postpartum. In the present study of women with moderate or severe pre-eclampsia, 26·5% had pleural fluid, which suggests that pleural effusions represent part of the syndrome of pre-eclampsia.

In most respects the women with pleural fluid did not differ from those without, particularly in the degree of proteinuria and degree of hypertension used to define the syndrome. No difference was seen in the degree of hypoalbuminaemia, and it is difficult to suggest that the effusions were the result of iatrogenic fluid overload, as there was no difference in the volumes of intravenous fluid given. Mode of delivery and forms of analgesia and anaesthesia did not differ between the groups. These data provide no clues to the aetiology of the effusion.

However, the presence of pleural fluid was associated with early severe disease resulting in earlier delivery. The shorter gestation of these babies was responsible for the neonatal deaths in this group; all the neonatal deaths were born at 27 weeks gestation with birthweights ranging from 680 to 820 g. Pleural fluid as a sign of early severe pre-eclampsia was associated with a perinatal mortality of 40%, tenfold greater than the 4% when pleural fluid was not present.

Horvath *et al.* (1985) reported a perinatal mortality of 5% for pre-eclampsia presenting before 32 weeks; they also found a significantly higher perinatal mortality in patients transferred from other hospitals. It is interesting to note that in our study 78% of the patients with effusions were in fact referred from other centres before delivery compared with only 24% of the other group.

In summary, postpartum pleural effusions occur as an abnormal finding in patients with pre-eclampsia. The aetiology of this is unknown but it is not apparently related to either the degree of proteinuria or hypertension. But it is associated with a considerably increased risk of preterm labour and associated infant mortality.

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Ultrasound and pulsed electromagnetic energy treatment for perineal trauma. A randomized placebo-controlled trial

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Summary. Ultrasound and pulsed electromagnetic energy therapies are increasingly used for perineal trauma sustained during childbirth. The study included 414 women with moderate or severe perineal trauma randomly allocated to receive active ultrasound, or active pulsed electromagnetic energy, or corresponding placebo therapies; the allocation was double-blind for each machine. Overall, more than 90% thought that treatment made their problem better. There were no clear differences between the groups in outcome either immediately after treatment, or 10 days or 3 months postpartum, other than more pain associated with pulsed electromagnetic energy treatment at 10 days. Bruising looked more extensive after ultrasound therapy but then seemed to resolve more quickly. Neither therapy had an effect on perineal oedema or haemorrhoids. The place of these new therapies in postnatal care should be clarified by further controlled trials before they become part of routine care.

As many as 70% of women suffer trauma to the perineum during vaginal delivery which is sufficiently severe to require surgical repair (Sleep *et al.* 1984). This trauma commonly causes pain and discomfort which may persist for months (Sleep & Grant 1987), particularly if the injury is extensive. Ultrasound and, to a lesser extent, pulsed electromagnetic therapy are increasingly being used in the first few days after delivery to treat this problem: in a telephone survey of 36 randomly selected consultant maternity units conducted in 1987 (Sleep & Grant 1988) ultrasound therapy was being used to treat perineal trauma in 15 (42%), and pulsed electromagnetic energy being used in 3 (8%).

The mechanisms by which therapeutic ultrasound may improve tissue repair and reduce pain have been reviewed by Dyson (1987). The few well-conducted controlled trials of the clinical efficacy of ultrasound have all been small (Partridge 1987), but there is evidence that ultrasound therapy is effective for some soft tissue injuries, such as tennis elbow (Binder *et al.* 1985), leg ulcers (Dyson *et al.* 1976; Roche & West 1984; McDiarmid *et al.* 1985; Callam *et al.* 1987), and following oral surgery (El Hag *et al.* 1985). Two small controlled trials of therapeutic

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ultrasound for perineal trauma have been incompletely reported (McLaren 1984; Creates 1987). Both suggest a reduction in pain associated with active treatment, and one reported more rapid dispersal of bruising. However, these two studies on their own do not provide a firm basis for practice.

Pulsed electromagnetic energy therapy is also claimed to improve wound healing and reduce pain. A number of possible mechanisms have been suggested (Hayne 1984) and a controlled trial of therapy for perineal trauma suggested that pulsed electromagnetic energy may accelerate resolution of bruising and healing (Bewley 1986; A. W. Bird, personal communication).

We report a randomized controlled trial comparing ultrasound and pulsed electromagnetic energy therapy with double-blind, placebo treatments begun within 24 h of delivery, for moderate or severe perineal trauma.

Patients and methods

The trial was conducted at the maternity unit of the Royal Berkshire Hospital. The study design and protocol were approved by the research and ethics committee for West Berkshire. Recruitment took place on the postnatal wards on weekdays (Monday to Friday). Women were eligible for entry to the trial if they (i) required operative vaginal delivery; or (ii) sustained perineal trauma involving extensive damage to the anal sphincter or damage to the rectal or anal mucosa; or (iii) developed severe perineal oedema, bruising or haematoma within 24 h of delivery. Eligibility was checked by the midwife researcher who then sought consent to participation before formal trial entry: 419 women were invited of whom 414 agreed to participate. At entry, basic descriptive data were recorded adjacent to the next available trial number. The correspondingly numbered, sealed, opaque envelope was then allotted, and this was later opened by the physiotherapist researcher. Once the seal was broken, the mother had entered the trial irreversibly and remained in the study for analysis regardless of subsequent management. Each envelope contained the random treatment allocation: first to either ultrasound or pulsed electromagnetic energy and second to a number which signified random allocation to either active or placebo therapy. Each machine had a specially fitted 12-number dial: eight settings were active and four placebo. The codes for the switches were arranged by the manufacturers (EMS Medical Supplies) and held in sealed envelopes until the end of the trial. These codes were changed at 2-monthly intervals to minimize the risk of the operator breaking the code and thereby introducing bias. The therapists were also checked for sensitivity to the vibration of the ultrasound transmitter (Therasonic 1030) and it was confirmed that they could not distinguish the active from the inactive mode. Each week the output of the machines was checked by a physiotherapist who worked in a different part of the hospital. The ultrasound was transmitted at an operating frequency of 3 MHz, an intensity of 0·5 W/cm^2 and a pulse interval of 1:4; treatment was given for 2 min to each area of trauma equal to the size of the transmitting head. EMS ultrasound couplant was used as recommended by the manufacturers. The pulsed electromagnetic energy (Megapulse) unit was set at an operating frequency of 27 MHz, a pulse repeat rate of 100 pulses/s and a pulse width of 65 μs, pulse ratio normal, the duration of each treatment was set at 10 min.

Therapy was started about 12 h (always within 24 h) after delivery, a maximum of three treatments being given during a 36-h period. Assessments before and within 2 h after treatment were made by the mother (in respect of perineal pain, using 10-cm linear analogue and categorical scales) and by the midwife co-ordinator who documented the extent of oedema, bruising and haemorrhoids and any analgesia required over the course of treatment. A further assessment of pain and healing was made by the mother and the community midwife 10 days after delivery. Finally a postal questionnaire, self-administered by the mother, assessed maternal morbidity 3 months postpartum. All assessments were made 'blind' to whether the treatment was active or placebo. In most cases the research midwife and community midwives also did not know which type of machine had been allocated.

There were two main hypotheses tested in the trial. The first was that ultrasound or pulsed electromagnetic energy therapy or both would reduce the frequency and severity of perineal pain on the 10th day after delivery. The second was that active treatment would reduce the time to resumption of sexual intercourse and increase the frequency of pain-free intercourse 3 months after delivery. The effects of the two therapies on perineal pain at other times, the use of oral analgesia, perineal oedema, bruising and haem-

Table 1. Description of the trial groups at entry

	Pulsed electro-magnetic energy (*n*=135)	Ultrasound (*n*=140)	Placebo (*n*=139)
Maternal age (years) mean [SD]	27·3 [4·2]	26·9 [4·5]	27·1 [5·3]
Primigravida *n* (%)	103 (76)	99 (71)	92 (66)
Gestational age (weeks) mean [SD]	39·8 [1·7]	39·8 [1·4]	39·9 [1·7]
Birthweight (g) mean [SD]	3291 [530]	3377 [445]	3402 [521]
Instrumental or breech delivery *n* (%)	91 (67)	90 (64)	103 (74)
Type of perineal injury *n* (%)			
1° or 2° perineal tear	21 (16)	24 (17)	24 (17)
Uncomplicated episiotomy	78 (58)	81 (58)	85 (61)
Episiotomy + 2° extension	26 (19)	27 (19)	21 (15)
Extension of episiotomy or tear through anal sphincter or rectal mucosa	6 (4)	6 (4)	5 (4)
Other	4 (3)	2 (1)	4 (3)
Perineal pain at trial entry *n* (%)			
None	5 (4)	8 (6)	8 (6)
Effective epidural	9 (7)	4 (3)	9 (7)
Mild	20 (15)	18 (13)	22 (16)
Moderate	70 (52)	79 (57)	70 (51)
Severe	31 (23)	30 (22)	29 (21)
Bruising at trial entry *n* (%)	68 (51)	82 (60)	74 (53)
Oedema at trial entry *n* (%)	45 (33)	52 (37)	42 (30)
Haemorrhoids at trial entry *n* (%)	28 (21)	33 (24)	33 (24)

orrhoids and maternal feelings of well-being were also examined.

A sample size of 400 women was prespecified. This was based on an expected prevalence of perineal pain 10 days after delivery in the placebo group of 50%. A trial of this size has an 80% chance of showing a statistically significant difference if active treatment reduces this prevalence by one third.

The results for the two placebo groups were so similar that they were amalgamated to give a single pooled placebo group of the same size as the two actively treated groups for the purpose of analysis. χ^2 and *t*-tests with one-way analysis of variance were used where appropriate. Confidence intervals for relative risks were calculated using the method recommended by Katz *et al.* (1978). Ten-day forms were returned for 129 (96%) women in the pulsed electromagnetic energy group, for 134 (96%) in the ultrasound group, and for 131 (94%) in the placebo group. Three-month questionnaires were returned by 124 (92%), 126 (90%) and 125 (90%) women respectively.

Results

Table 1 describes the women who joined the study and demonstrates the comparability of the groups at trial entry. Overall, 69% had been delivered by forceps, vacuum extraction or assisted breech delivery; 18% had extensions of an episiotomy and a further 4% had third-degree perineal trauma; 79% had moderate or severe perineal pain at the time of recruitment.

All women received the allocated treatment. Women in the pulsed electromagnetic energy groups received three treatments each of 10 min duration, except for two women allocated to active pulsed electromagnetic energy who had two treatments each for 10 min. All women allocated ultrasound received three treatments. Duration of treatment in the ultrasound groups was more variable, the total ranging from 6 to 18 min; the mean duration in the actively treated group was 8·2 (SD 3·1) min, and in the placebo ultrasound group 7·5 (SD 3·0) min. Two women in the active ultrasound group had further active ultrasound therapy a few days after the trial regimen had been completed.

Table 2. Post-treatment assessment

	Pulsed electromagnetic energy (n=135)		Ultrasound (n=140)		Placebo (n=139)	
	n	(%)	n	(%)	n	(%)
Mother's assessment						
A little worse or no better	11	(8)	10	(7)	15	(11)
A little better	75	(56)	70	(50)	73	(53)
A lot better	49	(36)	60	(43)	50	(36)
Pain-free	17	(13)	17	(12)	17	(12)
Improvement in linear analogue pain rating (if pain at pretreatment assessment) (mm) mean [SE]	21·6	[1·9]	25·3	[1·8]	21·1	[2·1]
Bruise-free	70	(52)	60	(44)	69	(54)
Mean reduction in bruise size (if bruised at first) (mm) mean [SE]	2·9	[0·9]	0·7	[0·8]	3·2	[0·8]*
Oedema-free	109	(81)	111	(80)	108	(78)
Haemorrhoid-free	107	(79)	114	(82)	108	(78)
Mean change in size (if haemorrhoid at first) (mm) mean [SE]	4·1	[0·7]	4·4	[0·8]	4·0	[0·7]

*P<0·05.

At the post-treatment assessment 91% of the participants felt that treatment had made them better; these rates were similar in the three groups (Table 2). The pattern of perineal pain, oedema and haemorrhoids was also similar, and the greater improvement in the linear analogue pain scale in the ultrasound group was not statistically significant (t=1·56; 0·1<P<0·2). However, the ultrasound group did have more bruising when assessed after treatment and showed significantly smaller reduction in the extent of bruising over the course of treatment compared with the placebo ultrasound group (t=2·21; P<0·05).

Women in the pulsed electromagnetic therapy group were more likely to report perineal pain than women in the other two groups when assessed 10 days after delivery (Table 3) (χ^2=6·14,d.f.2, P<0·05, relative risk compared with placebo group = 1·4 [95% CI 1·0 to 2·1]). At that time the ultrasound group had the lowest prevalence of bruising but this difference was not statistically significant (relative risk compared with placebo group = 0·8, 95% CI 0·4 to 1·5).

Of the women who returned 3-month questionnaires, 57 (15%) still had perineal pain but there were no statistically significant differences between the trial groups (Table 4; relative risk compared with placebo group for pulsed electromagnetic energy group = 1·1 [95% CI 0·6 to 1·9], and for ultrasound = 0·6 [95% CI 0·3 to 1·2]). Similarly, rates of dyspareunia, urinary incontinence (overall prevalence 16%), faecal incontinence (overall prevalence 4%) and women's general feelings of well-being did not differ between the groups.

Discussion

The women who participated in this trial were indeed at high risk of persistent perineal pain as judged by their prevalence rates of pain. Compared with a series of 1000 women who had normal deliveries (Sleep *et al.* 1984) the rates at 10 days and at 3 months after delivery were three times (66% *vs* 23%) and two times (15% *vs* 8%) higher respectively. Randomization generated comparable groups at entry. There was no possibility of concealing from the mothers which type of treatment machine was used although in most cases the research midwife and community midwives were 'blind'. But the precautions taken to 'blind' the active treatments were successful and the strength of a placebo-controlled study is illustrated by the fact that over 90% of women in all groups thought that 'treatment' had done some good. Treatment was given early for the

Table 3. Outcome 10 days after delivery

	Pulsed electro-magnetic energy (*n*=129)		Ultrasound (*n*=134)		Placebo (*n*=131)	
	n	(%)	*n*	(%)	*n*	(%)
Perineal pain in last 24 h* (reported by mother)						
None	33	(26)	53	(40)	48	(37)
Mild	57	(44)	50	(37)	44	(34)
Moderate	30	(23)	24	(18)	33	(25)
Severe	9	(7)	7	(5)	6	(5)
Use of pain-killers in previous 24 h	31	(24)	30	(22)	25	(19)
Community midwife's assessment						
Perineal wound breaking down	6	(5)	6	(4)	3	(2)
Haemorrhoids	33	(26)	35	(26)	33	(25)
Bruising	22	(17)	14	(10)	18	(14)
Oedema	13	(10)	10	(7)	11	(8)

*$P<0.05$.

practical reason that many women leave hospital after 2 days, and also because it was felt that early treatment might prevent problems in the longer term. Women in the pulsed electromagnetic energy group had more pain 10 days after delivery but there were no statistically significant differences between the groups at 3 months postpartum.

Bruising tended to be more extensive immediately following ultrasound therapy (Table 2) but also seemed to disappear more rapidly thereafter (Table 3). This latter finding is consistent with claims made about ultrasound and with the controlled study reported by McLaren (1984). This pattern was not seen in the placebo ultrasound group so is likely to be a consequence of ultrasound treatment rather than perineal massage during therapy. We were surprised by these findings of no clear benefit of active therapy, particularly in respect of ultrasound because this therapy has been shown to be effective for some other soft tissue injuries and because we were impressed by its apparent efficacy before the trial. A possible explanation is that we chose the wrong operating frequencies, intensities or pulse intervals. Nevertheless, the settings used in the trial are in line with current practice as judged by the replies to an informal survey of senior physiotherapists made by one of us (J.M.) before the trial commenced.

Because we wished to assess whether the treatment modalities are useful in this context we did not include a 'no treatment' group. If we had, we might have demonstrated an important

Table 4. Outcome 3 months after delivery

	Pulsed electro-magnetic energy (*n*=124)		Ultrasound (*n*=126)		Placebo (*n*=125)	
	n	(%)	*n*	(%)	*n*	(%)
Perineal pain (worst pain in last week)						
None	101	(82)	113	(90)	104	(83)
Mild	14	(11)	6	(5)	20	(16)
Moderate	8	(7)	7	(6)	1	(1)
Severe	1	(1)	0	(0)	0	(0)
Resumed sexual intercourse	101	(81)	93	(74)	100	(80)
Pain-free sexual intercourse	41	(33)	33	(26)	37	(30)

placebo effect resulting from extra attention from a physiotherapist in the first 48 h after delivery.

More than 40% of consultant obstetric units now have access to therapeutic ultrasound or pulsed electromagnetic energy treatment or both (Sleep & Grant 1988). In the light of the results presented here, current enthusiasm for the new therapies should be tempered. Further controlled trials are needed; first to replicate our design; second to assess different machine settings and length of treatment; and third to assess the usefulness of ultrasound and pulsed electromagnetic energy in other obstetric settings.

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The excretion of 5-oxoproline in urine, as an index of glycine status, during normal pregnancy

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Summary. The urinary excretion of 5-oxoproline, which may be used as an index of glycine status, was investigated in 30 normal pregnant women during different stages of pregnancy and in 18 non-pregnant female volunteers. During an 18-h study there was little variation in the 5-oxoproline/creatinine index, and a single sample gave a representative value. The excretion of 5-oxoproline/creatinine (μmol/mmol) rose progressively as pregnancy advanced (non-pregnant mean 10, SD 5, first trimester mean 46, SD 12, second trimester mean 150, SD 180, and third trimester mean 280, SD 320) and by the third trimester was over 20 times greater than in non-pregnant women. The data suggest that as pregnancy advances the endogenous production of glycine may be insufficient to satisfy the increasing demands.

The pregnant woman has to ingest sufficient nutrients to satisfy the additional demands of fetal growth and elaboration. One remarkable feature of this is the unusual requirement for particular amino acids, especially glycine. The rate of accumulation of glycine by the rapidly growing fetus is very high, being two to 10 times that of other amino acids on a molar basis (Widdowson *et al.* 1979). It is unlikely that this unusual pattern of demand of amino acids can be satisfied by the habitual dietary intake. Although under normal circumstances the body is able to synthesize sufficient glycine to satisfy a shortfall, this ability is limited and may not always keep pace with a large imbalance between the dietary intake and the metabolic demand (Yu *et al.* 1985). Recently we reported that an increase in the urinary excretion of 5-oxoproline might, under appropriate circumstances, act as an index of glycine insufficiency (Jackson *et al.* 1987).

5-oxoproline (pyroglutamic acid, pyrrolidone carboxylic acid) is a normal metabolic intermediary as a component of the γ-glutamyl cycle described by Meister (1978). In normal, healthy individuals 5-oxoproline is excreted at a low level in urine. Excessive rates of excretion of 5-oxoproline have been reported in congenital deficiencies of the enzyme glutathione synthetase (Wellner *et al.* 1974) which catalyses the formation of glutathione from γ-glutamylcysteine and glycine. If the body pool of glycine is depleted by the ingestion of large amounts of benzoic acid to form hippuric acid, the excretion of 5-oxoproline in urine is increased (Fig. 1), presumably because flux through glutamate synthetase is impaired (Jackson *et al.* 1987). Therefore, the urinary excretion of 5-oxoproline might be used as a non-invasive index of glycine status.

We reasoned that during pregnancy the endogenous synthesis of glycine might be insufficient to satisfy the unusual demands for fetal growth.

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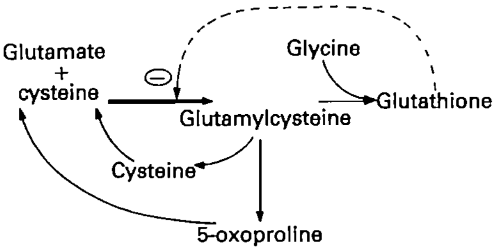

Fig. 1. Glutathione controls its own rate of production by feedback inhibition on the first reaction leading to its formation. A limited supply of glycine leads to a reduced formation of glutathione, which in turn releases the inhibition on the production of glutamylcysteine from glutamate and cysteine. As the glutamylcysteine cannot be converted to glutathione quantitatively, it follows an alternative metabolic pathway whereby the glutamyl residue forms 5-oxoproline.

If this were so, then the excretion of 5-oxoproline in urine would be expected to increase. In this study we have measured the excretion of 5-oxoproline at different stages in pregnancy and compared it with that in a control group of non-pregnant women.

Subjects and methods

The study included 30 pregnant women with uncomplicated medical histories who were attending the antenatal clinic of the University Hospital of the West Indies. The women were invited to participate after the purpose and nature of the study had been explained to them. Control subjects were recruited from the nursing and the scientific staff. The study had the approval of the ethics committee of the University Hospital of the West Indies.

The study was conducted in two phases. In the first phase urine was collected at intervals of 3 h for 18 h in six non-pregnant women and in six women at 12 weeks gestation. The diurnal pattern of 5-oxoproline excretion was identified, and compared with a single morning urine collected from 12 non-pregnant women. In the second phase of the study, single morning specimens were collected from 12 women during the second trimester and 12 women during the third trimester of pregnancy.

Urine was collected into 500 µl of 12 N HCl and was stored at −4°C until analysis. Under these conditions 5-oxoproline is stable and there is no conversion of glutamic acid or glutamine to 5-oxoproline (Shih 1985). The method of McPherson & Slater (1959) was used to measure 5-oxoproline, in which 5-oxoproline is first converted to glutamic acid by acid hydrolysis and the glutamic acid measured enzymatically. For the analysis, 2 ml of the acidified urine was added to 2 ml of perchloric acid, 100 g/l. After centrifugation, 1 ml of the supernatant was diluted wth 4 ml of water, and 2 ml of this solution were added to 2 ml of 6 N HCl and heated at 100°C for 3 h. The solution was then heated to dryness and the residue was reconstituted with 2 ml of Tris-hydrazine buffer, pH 9. The glutamic acid content was measured using glutamate dehydrogenase (EC 1.4.1.2, Sigma Chemical Co., USA) as described by Bernt & Bergmeyer (1974). The glutamic acid content of urine before and after acid hydrolysis was measured, and the difference between the two taken as a measure of 5-oxoproline in the urine. The creatinine in urine was measured by the alkaline picrate method of Jaffe as described by Bonsnes & Taussky (1945), after pretreatment of the urine with Lloyd's reagent to remove interfering chromogens.

The Mann–Whitney test was used to identify significant differences between groups (Snedecore & Cochran 1967).

Results

In both the non-pregnant and the pregnant women there was little in the way of a diurnal variation in the rate of 5-oxoproline excretion over the 18-h period (Figs 2 & 3). Figure 2 shows that when the excretion of 5-oxoproline is expressed as a ratio to urinary creatinine, the mean excretion in normal women was 11 (SD 5) µmol/mmol. The mean urinary 5-oxoproline in the single samples was 7 (SD 4) µmol/mmol, not significantly different. The results from these 18 women gave an upper limit to the normal range (mean +2 SD) of 18 µmol/mmol. By 12 weeks gestation there was a fourfold increase in the urinary excretion of 5-oxoproline on average, to 46 µmol/mmol creatinine ($P<0\cdot01$) (Fig. 3).

The rates of excretion of 5-oxoproline during the second and third trimesters of pregnancy are shown in Table 1. During the second trimester the mean rate of excretion had increased 10 to 15 times the control value, to 150 µmol/mmol ($P<0\cdot01$), with a great increase in the range of values. By the third trimester there was more than a 20-fold increase in 5-oxoproline excretion with the range going from 12 to 1210 µmol/mmol

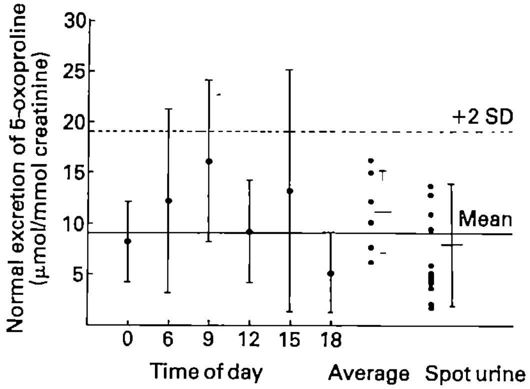

Fig. 2. Urinary excretion of 5-oxoproline (μmol/mmol creatinine) in six normal, non-pregnant women (mean values and standard deviation represented by vertical bars). There was little variation in the excretion of 5-oxoproline in the six women over the 18 h. The mean excretion over 18 h for each woman (11·0, SD 5) is shown, and as a group these were not significantly different from the excretion in a single early morning urine from a further group of 12 women (7·0, SD 4).

creatinine ($P<0{\cdot}01$). The rate of excretion in the third trimester was significantly greater than that in either the first ($P<0{\cdot}01$) or the second trimester ($P<0{\cdot}05$).

Discussion

It is recognized that the renal handling of amino acids is altered during pregnancy, as the glomerular filtration rate increases and tubular resorption is less efficient. The extent to which different amino acids appear in the urine varies. For most amino acids there may be a doubling in the rate of excretion, with the maximal change being six to eight times normal (Wallraff *et al.* 1950; Hytten & Cheyne 1972). The excretion of creatinine may also increase as gestation advances. As a consequence of these changes, although the absolute excretion of amino acids may increase, the relative rates of excretion remain fairly constant, or fall, when expressed as a ratio to creatinine excretion. It therefore seems reasonable to express the rate of excretion of 5-oxoproline relative to that of creatinine.

Our data demonstrate that in normal women the urinary excretion of 5-oxoproline is low, and that the rate of excretion changes little during the day. During normal pregnancy there is an increase in the rate of 5-oxoproline excretion which can be identified as early as 12 weeks gestation. The increase in excretion is more pronounced in the urine of women at progressively later stages of pregnancy. In a cross-sectional study it is not possible to say whether this increase with advancing pregnancy represents an increase in the intra-individual, or inter-individual variation, but at all stages of pregnancy the excretion of 5-oxoproline exceeded that in the non-pregnant women. If 5-oxoprolinuria can be used as an index of glycine status in this situation, then the observations support the thesis that glycine availability becomes increasingly compromised as the fetal demands increase with advancing pregnancy.

The chemical structure of 5-oxoproline, as a ninhydrin-negative lactam of glutamic acid, means that it is not retained on a negatively charged ion resin, and thus is not detected in the usual methods of amino acid analysis (Wolfersberger & Tabachnik 1973). Therefore, in order to detect the compound we had to resort to special techniques. It is possible to get an increase in urinary 5-oxoproline associated with an increased dietary intake, or through the activity of the gastrointestinal microflora. However, in both of these situations it is the 5-D-oxoproline which is excreted rather than the metabolically active L-isomer. As the enzyme assay will only measure the L-isomer, it is unlikely that the changes we have observed can be accounted for by either of these possibilities.

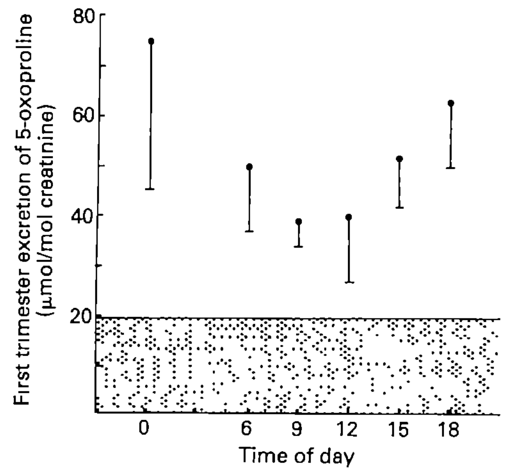

Fig. 3. Urinary excretion of 5-oxoproline (μmol/mmol creatinine) in six women during the first trimester of pregnancy (mean value and standard deviation represented by vertical bars). The shaded area represents the mean +2 SD for the non-pregnant group. The mean excretion in women during the first trimester (46·0, SD 12·0) was significantly greater than in the non-pregnant group ($P<0{\cdot}01$)

Table 1. The excretion of 5-oxoproline (μmol/mmol creatinine) in non-pregnant women and in women during the first, second and third trimesters of pregnancy

		5-oxoproline (μmol/mmol creatinine)			
	Number	Median	Range	Mean	(SD)
Non-pregnant	18	10	2–30	10	(5)
First trimester	6	47	28–62	46*	(12)
Second trimester	12	96	21–680	150*	(180)
Third trimester	12	212	12–1210	280*†	(320)

Significant differences: $^*P<0{\cdot}01$ compared with non-pregnant; $^\dagger P<0{\cdot}05$ compared with second trimester.

In theory, a change in 5-oxoproline excretion could be a consequence of altered function of either of the enzymes glutathione synthetase or 5-oxoprolinase. Under normal circumstances the capacity of both these enzymes greatly exceeds the level of activity required for normal function, and it seems unlikely that either is sufficiently impaired to account for our findings. Indeed, in the rat the evidence suggests that both fetal and maternal tissues develop an enhanced capacity to synthesize glutathione as pregnancy advances (Di Ilio *et al.* 1985, 1986). In other situations where rapid growth increases the demand for glycine, we have found increased rates of 5-oxoproline excretion. In children recovering from severe malnutrition, supplemental dietary glycine served to reduce the urinary excretion of 5-oxoproline (Persaud *et al.* 1987).

Therefore, we have been able to produce evidence in support of the suggestion that in some women the endogenous synthesis of glycine may be inadequate to satisfy the increased needs of pregnancy. On the basis of a single urine analysis it would seem that there is a considerable range of variability between women. It remains for future work to determine whether this variation represents a transient phenomenon in all women or a persistent state in some women, and whether or not 5-oxoproline bears any association with fetal or neonatal well-being. Any consideration of glycine supplementation would be inappropriate until this information is available.

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The relation between daily salivary progesterone profile and endometrial development in the luteal phase of fertile and infertile women

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Summary. This study analysed the relation between daily salivary progesterone profiles in the luteal phase and endometrial development as assessed by morphometric studies of endometrial biopsies that were timed by luteinizing hormone surge. Among 34 fertile women studied, a threshold relation was noted between cumulative salivary progesterone concentration and 11 of the 17 morphometric features measured, as well as the results of the histological dating. Above the observed threshold, a significant linear correlation was found between cumulative salivary progesterone and the results of histological dating. Among 55 women, the progesterone profile in the first half of the luteal phase, but not the second half, was found to be significantly lower in those with retarded endometrial development than in those with normal development. Overall, 50% of retarded endometrial development was associated with a subnormal progesterone profile, but the other 50% was associated with a normal progesterone profile, in keeping with an abnormal response of the endometrium due to progesterone receptor deficiency. Retarded endometrial development was more likely to be associated with a subnormal progesterone profile in the first half of the luteal phase than in the second half.

Both the measurement of plasma progesterone and endometrial biopsy are common investigations in infertility practice. When these two methods were used to establish whether or not ovulation had occurred, the agreement reached between them was found to be 90–93% by Nadji *et al.* (1975) and Rosenfeld & Garcia (1976), using a plasma progesterone level of 2 ng/ml in the mid-luteal phase as the cut-off point between ovulation and anovulation. On the other hand, when these two methods have been used to assess the quality of the luteal phase, conflicting results have been reported. Some authors (Gautray *et al.* 1981; Cook *et al.* 1983) found that in women with retarded endometrial development of more than 2 days, the mid-luteal plasma progesterone levels were significantly lower than in those with normal endometrial development. But many other investigators found no difference in the plasma progesterone levels taken in the luteal phase between women with normal or retarded endometrial development (Rosenfeld *et al.* 1980;

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Balasch *et al.* 1982; Haciski *et al.* 1983), or a lack of significant correlation between these two methods in the assessment of corpus luteum function (Cooke *et al.* 1972; Shepard & Senturia 1977; Annos *et al.* 1980; Shangold *et al.* 1983).

We hypothesized that the controversy was due to a lack of precision in the measurement of endometrial development, or progesterone assay, or both. We therefore designed a prospective study to examine the relation between endometrial development and progesterone concentration in the luteal phase by the use of more precise methods of dating endometrium: using the luteinizing hormone (LH) surge for chronological dating of endometrial biopsies (Li *et al.* 1987), and morphometric analysis for histological dating (Li *et al.* 1988), as well as the use of daily salivary progesterone measurement throughout the whole luteal phase, instead of a single progesterone measurement. Initially, the relation was analysed in a homogeneous, fertile sample of women. Infertile women were excluded from the initial analysis because a certain proportion of them may have a progesterone receptor deficiency, leading to a poor response of the endometrium to circulating progesterone, and consequently a poor correlation between these two measurements (Cooke *et al.* 1972; Keller *et al.* 1979).

In addition, we attempted to analyse further the relation between retarded endometrial development and progesterone profile by addressing two questions. First, is the salivary progesterone profile in those with retarded endometrial development different from those with normal endometrial development? Second, how frequently is retarded endometrial development due to subnormal progesterone production from the corpus luteum?

Subjects and methods

Both fertile and infertile women were included in this study, but they were analysed separately. All the women included in the study fulfilled the following inclusion criteria. (i) An endometrial biopsy obtained in the luteal phase, which was timed prospectively by LH surge as the basis of accurate chronological dating. (ii) Complete daily saliva collection from late proliferative phase through to the end of the luteal phase. (iii) No treatment in the follicular or luteal phase that may have an influence on endometrial morphology or circulating steroid hormone levels.

Fertile women

Normal fertile women were recruited from those attending the gynaecological outpatient clinic of the University Department of Obstetrics and Gynaecology at the Jessop Hospital for Women, Sheffield, between February 1986 and May 1987. Most of them attended with a request for sterilization or reversal of sterilization. Normal fertile women were defined as those who had regular cycles of 25–35 days, had not received any steroid hormones (including oral contraceptive) or used an intrauterine contraceptive device for at least 3 months, were aged between 18 and 40 years, had no known history of menstrual disorder and had one or more successful pregnancies in the past.

Infertile women

Women with unexplained infertility (infertility of more than 1 year, with normal, regular sexual intercourse, documented evidence of ovulation, normal hysterosalpingogram, laparoscopy, semen analysis, thyroid function test and prolactin) who fulfilled all but the last of the above mentioned inclusion criteria (for fertile women) and who attended the clinic between February 1986 and May 1987, were included in the study.

Salivary progesterone assay

Women participating in the study were given a pack of 28 tubes contained in a box and asked to start collecting daily samples of saliva from day 9 of the cycle. Progesterone concentration in the saliva was determined by a direct radioimmunoassay method, using ^{125}I-labelled progesterone (ER-205, Steranti Research Laboratory Ltd, UK), similar to that described by Chearskul *et al.* (1982).

Endometrial biopsy

Endometrial biopsies were obtained from outpatients. Using a Sharman's curette (Downs Surgical Ltd, Sheffield, UK) a single endometrial specimen was obtained from the fundus and upper part of the body of the uterus. Each specimen was fixed immediately in 2% glutaraldehyde in cacodylate buffer (pH 7·4) for 4–6 h. It was then washed in buffer, dehydrated and embedded in JB-4 (Polysciences, Inc., USA), a plastic polymer. The specimen was sectioned at 2 μm, and the sections were stained with acid fuchsin and toluidine blue for examination by light microscopy.

All the biopsies were timed by the LH surge. The day of the LH surge (designated LH+0) was determined by daily LH assay on a specimen either of morning urine or of plasma, starting on day 9 of the menstrual cycle (Li *et al.* 1987).

All the endometrial biopsies were studied histologically by one observer, who was unaware of the chronological dating at the time of the study. Two different methods were used; one method used the dating criteria of Noyes *et al.* (1950) and the other used a morphometric analysis, in which a total of 17 morphological features were measured for each endometrial biopsy, which were the following.

Gland. G1, number of mitoses per 1000 gland cells; G2, gland cell height (μm); G3, amount of secretion in gland lumen (score 0 to 3); G4, maximal gland diameter (μm); G5, volume fraction of gland occupied by gland cell; G6, volume fraction of endometrium occupied by gland; G7, volume fraction of gland cell occupied by nucleus; G8, number of supranuclear secretory vacuoles per 100 gland cells; G9, number of subnuclear vacuoles per 100 gland cells; G10, amount of pseudostratification of gland cells (score 0 to 3); G11, number of apoptotic bodies (Hopwood & Levison 1976) per 1000 gland cells.

Stroma. S1, number of mitoses per 1000 stromal cells; S2, amount of stromal oedema (score 0 to 3); S3, amount of predecidual reaction (score 0 to 3); S4, diameter of venule (μm); S5, amount of leucocytic infiltration (score 0 to 3); S6, amount of extravasation (score 0 to 3).

The methods used for morphometric measurements included point counting, cell counting, linear measurement (Williams 1977) and semiquantitative measurement (Johannisson *et al.* 1982). The statistical method used to perform histological dating based on the results of morphometric analysis has been described previously (Li *et al.* 1988).

Definitions

Cumulative salivary progesterone concentration. It was assumed that endometrial development in the luteal phase bore a better relation to the total progesterone output by the corpus luteum up to the time when the biopsy was obtained than to a single progesterone measurement on the day of the biopsy. Thus, for each biopsy, a cumulative salivary progesterone concentration was derived by adding up the daily salivary progesterone concentration from day LH+1 to the day of the biopsy, inclusive. This cumulative concentration was used to investigate the possible association with endometrial development.

Normal progesterone profile. The normal progesterone profile may be defined from the daily progesterone concentrations (with which multiple comparisons would be necessary), or the cumulative progesterone concentration as defined above. For the purpose of this study, in order to avoid the problems of multiple comparisons, the latter method was used. In addition, the profile (cumulative progesterone concentration) was defined as subnormal if it fell below the 5th centile of those that had resulted in normal endometrial development, as assessed by morphometric analysis ($n = 43$).

Normal endometrial development. To define normal endometrial development by morphometric analysis, a sample of 70 endometrial biopsies collected from fertile women (Li *et al.* 1988) was used. The normal reference range (2·5–97·5 centile) of the difference between histological dating by morphometric analysis and chronological dating was used to define normal endometrial development: this corresponded to −1·8 and +1·6 days. Thus, retarded endometrial development was defined as histological dating more than 1·8 days behind chronological dating, and advanced endometrial development was defined as histological dating more than 1·6 days ahead of chronological dating.

Results

A total of 34 normal fertile women was recruited into the study; their mean age was 34·4 years (SD 2·9, range 28–39). In addition, 21 women with unexplained infertility were included in the study; their mean age was 33·2 years (SD 4·6, range 24–44).

Relation between endometrial development and daily salivary progesterone profiles in normal fertile women

In this analysis, the possible association of endometrial development and progesterone profiles was investigated without any reference to normality or abnormality. Thus, all the 34 fertile women who were recruited were included in the analysis and none was excluded on the grounds of abnormal endometrial development or progesterone profile. In Fig. 1 the 17 morphometric measurements are plotted against the cumulative salivary progesterone concentrations. These graphs show that varying strengths of relation existed between the individual morphometric measurements and cumulative salivary progesterone concentration.

In some measurements there appeared to be a threshold of cumulative salivary progesterone, below which the morphometric measurements altered little with change in cumulative salivary progesterone concentration, but above which rapid increase in morphometric measurements occurred with increase in cumulative salivary progesterone concentration. For G3 and G4, such a threshold occurred around a cumulative salivary progesterone concentration of 300 pmol/l; for G8 and G9, it occurred around 200 pmol/l; whereas for G11, S3, S5 and S6, it occurred around 1000 pmol/l.

As for G1, S1 and G10, where the measurements appeared to decrease with increasing concentration of cumulative salivary progesterone, it is apparent that above a cumulative salivary progesterone concentration of around 1000 pmol/l, the measurements reached their lowest limit, and therefore could no longer show any change with further increase in cumulative salivary progesterone concentration.

For the remaining six measurements, the presence of a threshold was not apparent. In these cases, their relation with log cumulative salivary progesterone concentrations was tested for the presence of linear correlation. Significant linear correlation was absent in G2, S2 and S4, but present in the remaining three (G5, $r = -0{\cdot}62$, $P < 0{\cdot}0001$; G6, $r = 0{\cdot}63$, $P < 0{\cdot}0001$; G7, $r = -0{\cdot}30$, $P < 0{\cdot}05$).

Instead of individual morphometric measurements, the result of histological dating according to morphometric analysis may be correlated to the cumulative salivary progesterone concentration. The result is shown in Fig. 2a. Again, a threshold was noted around a cumulative salivary progesterone concentration of 300 pmol/l, below which the histological dating seemed little influenced by cumulative salivary progesterone concentration, but above which the histological dating changed rapidly with alteration in cumulative salivary progesterone concentration. For comparison, the result of histological dating by the criteria of Noyes *et al.* (1950) was also correlated to the cumulative salivary progesterone concentration (Fig. 2b). The same threshold was also observed around a cumulative salivary progesterone concentration of 300 pmol/l.

Above this threshold, there was a significant linear correlation between cumulative salivary progesterone concentration and the results of histological dating (morphometric analysis, $r = 0{\cdot}72$, $P < 0{\cdot}001$; criteria of Noyes *et al.* (1950), $r = 0{\cdot}56$, $P < 0{\cdot}001$).

Progesterone profile in those with retarded endometrial development

This analysis included the 34 fertile and also the 21 infertile women. When morphometric analysis was used to assess endometrial development, four of these 55 women had endometrial development that was considered to be advanced and they were excluded from further analysis. Among the remaining 51 women, the salivary progesterone profiles throughout the luteal phase of those with normal ($n = 43$) and retarded ($n = 8$) endometrial development were compared by using the two-sample t-test on log-transformed data for each day from days LH+1 to LH+14. The results given in Fig. 3a illustrate first that the mean daily salivary progesterone profile was consistently lower in those with retarded than in those with normal endometrial biopsies, and second that the differences between the two groups were significant only from day LH+3 to LH+7, but not before LH+3 or after LH+7.

It is of interest to compare the result when the criteria of Noyes *et al.* (1950) were used for histological dating. In this case, retarded endometrial development was defined as histological dating of more than 2 days behind chronological dating (Wentz 1980; Rosenberg *et al.* 1980; Balasch *et al.* 1982; Downs & Gibson 1983; Cumming *et al.* 1985). Using such criteria, the salivary progesterone profiles between the two groups with normal ($n = 43$) and retarded ($n = 6$) endometrial biopsies were compared, using two-sample t-tests (the remaining six women with advanced development were not included in the analysis). The results are plotted in Fig. 3b and show that there was no longer any significant difference in salivary progesterone, on any of the days in the luteal phase, between the two groups.

To find out how frequently retarded endometrial development is associated with subnor-

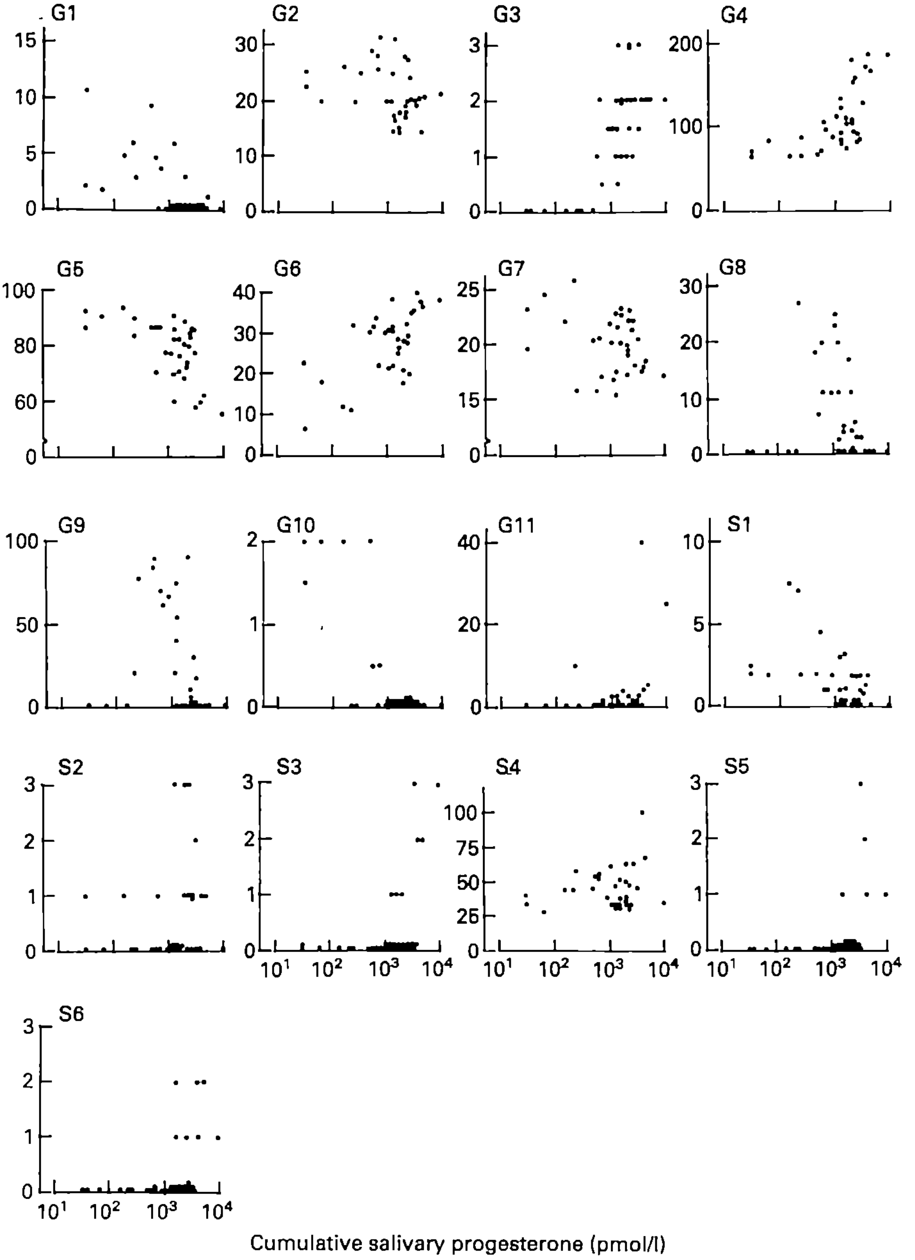

Fig. 1. The relation between cumulative salivary progesterone concentration (see text for definition) and individual morphometric measurements. G1, Number of mitoses per 1000 gland cells; G2, gland cell height (μm), G3, amount of secretion in gland lumen (score 0 to 3); G4, maximal gland diameter (μm); G5, volume fraction of gland occupied by gland cell (%), G6, volume fraction of endometrium occupied by gland (%); G7, volume fraction of gland cell occupied by nucleus (%), G8, number of supranuclear secretory vacuoles per 100 gland cells; G9, number of subnuclear vacuoles per 100 gland cells; G10, amount of pseudostratification of gland cell (score 0 to 3); G11, number of apoptotic bodies per 1000 gland cells; S1, number of mitoses per 1000 stromal cells, S2, amount of stromal oedema (score 0 to 3); S3, amount of predecidual reaction (score 0 to 3); S4, diameter of venule (μm); S5, amount of leucocytic infiltration (score 0 to 3); S6, amount of extravasation (score 0 to 3).

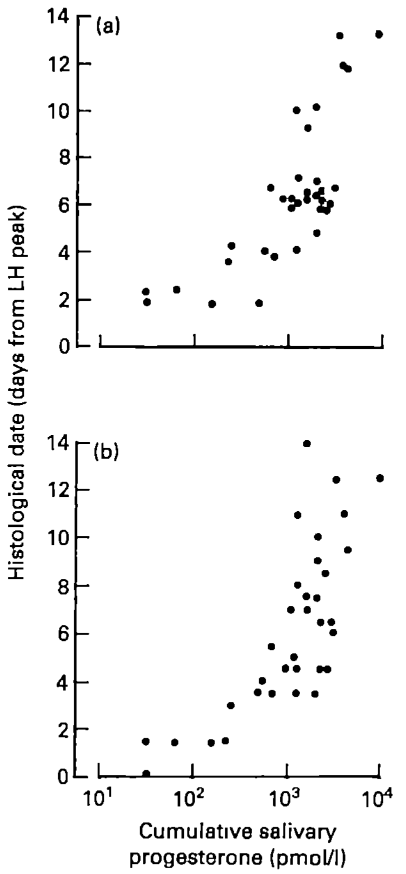

Fig. 2. The relation between cumulative salivary progesterone concentration and histological dating by (a) morphometric analysis and (b) the criteria of Noyes *et al.* (1950). In both cases, a threshold is noted around a cumulative salivary progesterone concentration of 300 pmol/l.

mal progesterone production from the corpus luteum, the relation between endometrial development and progesterone profile was further analysed (Table 1). Of the eight women with retarded endometrium, only four (50%) had subnormal salivary progesterone profiles, whereas the other four (50%) would be considered to have normal salivary progesterone profiles, capable of producing normal endometrial development.

However, as the results in Fig. 3 suggested that the relation between endometrial development and salivary progesterone profile in the first half of the luteal phase may be different from that of the second half, the results were further analysed for the first and second half of the luteal phase separately (Table 1). There was again a striking difference between the two halves of the luteal phase. All three retarded endometrial biopsies obtained in the first half were associated with subnormal salivary progesterone profiles, whereas only one of five obtained in the second half was associated with a subnormal salivary progesterone profile.

Discussion

Relation between endometrial development and progesterone profile in a fertile population

Our results show that endometrial development has a good correlation with corpus luteum function as measured by daily salivary progesterone.

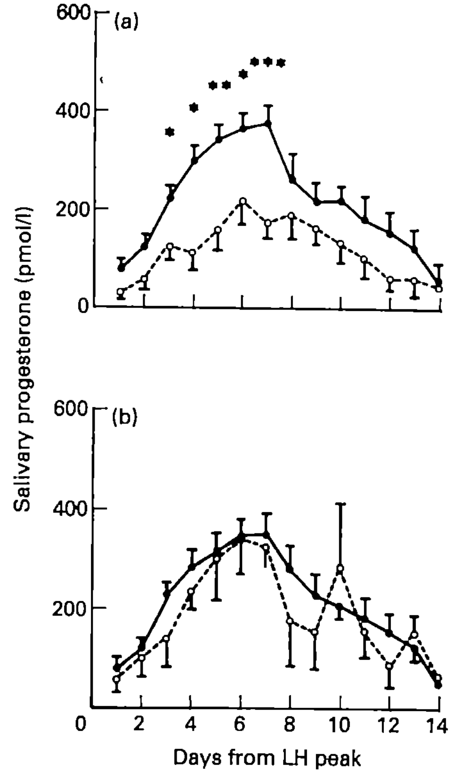

Fig. 3. The profile of daily salivary progesterone concentration (mean±SE) in those with normal endometrial development (——●——) and those with retarded endometrial development (– –○– –). * $P<0{\cdot}05$; ** $P<0{\cdot}01$; *** $P<0{\cdot}001$. (a) Morphometric analysis was used to define normal ($n = 43$) or retarded ($n = 8$) endometrium. (b) The criteria of Noyes *et al.* (1950) were used to define normal ($n = 43$) or retarded ($n = 6$) endometrium.

Table 1. Two-by-two contingency tables showing the relation between normal and retarded endometrial development, and normal and subnormal cumulative salivary progesterone profile (definition, see text) in all 51 samples and separately for the first and second half of the luteal phase

	Endometrial development	
Salivary progesterone	Normal	Retarded
(A) All samples (Days LH+1 to LH+14)		
Normal	40	4
Subnormal	3	4
(B) First half (Days LH+1 to LH+7)		
Normal	28	0
Subnormal	3	3
(C) Second half (Days LH+8 to LH+14)		
Normal	12	4
Subnormal	0	1

Significance: (A) $\chi^2 = 7{\cdot}2$ (after Yates' correction) $P<0{\cdot}01$
(B) $\chi^2 = 9{\cdot}9$ (after Yates' correction) $P<0{\cdot}01$.
(C) Fisher's exact test $P = 0{\cdot}29$.

This is in contrast to the lack of correlation between endometrial development and circulating progesterone concentration reported by some earlier investigators. There are several reasons to account for their results. First, many of these previous investigators used only a single plasma progesterone assay to measure corpus luteum function, whereas in our study, progesterone concentration was measured daily throughout the luteal phase from which the cumulative salivary progesterone concentration was derived. It is likely that the latter is a more accurate method of measuring corpus luteum function than a single progesterone measurement.

Second, most of the previous investigators used the onset of the next menstrual period as the basis of chronological dating of the endometrial biopsy. This has introduced an undesirably large variance in the chronological dating of the endometrial biopsy (Li *et al.* 1987). In the present study, all the biopsies were timed more precisely using the LH surge.

In addition, all previous investigators, except Johannisson *et al.* (1982), used the subjective dating criteria of Noyes *et al.* (1950) to measure endometrial development. Johannisson *et al.* (1982) were the first to use morphometric analysis and demonstrated significant correlation between glandular diameter and the mean level of progesterone in the plasma of the preceding 72-h period, throughout the luteal phase ($r = 0{\cdot}48$, $P<0{\cdot}01$). In our study, the equivalent measurement is G4. If we assume the relation between this measurement and cumulative salivary progesterone concentration to be linear, a significant correlation is found ($r = 0{\cdot}64$, $P<0{\cdot}0001$). However, as a threshold of cumulative salivary progesterone concentration of around 300 pmol/l is observed in G4, we think that simple linear regression analysis in this case may not be the best method to describe the relation.

The observation that a threshold level of cumulative salivary progesterone concentration exists for many of the morphometric measurements, and for histological dating, above which rapid change starts to occur, suggests that it is likely to be a true biological phenomenon. It therefore introduces the important concept that there is a minimum cumulative amount of circulatory progesterone required in order to trigger many of the morphological changes typical of the secretory phase of the menstrual cycle.

Progesterone profile in those with retarded endometrial development

It is of interest to note that the difference in salivary progesterone profile between those with normal and retarded endometrial development was statistically significant only from days LH+3 to LH+7, but not on other days of the luteal phase. Although the reason for this is unknown, such a new finding suggests that the amount of progesterone produced by the corpus luteum from days LH+3 to LH+7 has a more critical influence on endometrial development than that produced on the other days of the luteal phase. This is supported by the findings of Cooke *et al.* (1977) who demonstrated that infertile women, when compared with women who were fertile, had significantly lower plasma progesterone concentrations in the first half, but not the second half, of the luteal phase.

On days LH+1 and LH+2 the amount of progesterone produced by the corpus luteum is small, but it increases rapidly from days LH+3 onwards to reach a maximum on days LH+7 and LH+8. It is during this period of rapid increase that endometrial development seems most sensitive to progesterone. On the other hand, in the absence of implantation which normally takes place around day LH+7 (Hertig *et al.* 1956), it seems that circulating progesterone concentration in the remaining half of the luteal phase has no longer any significant predictive value for the subsequent development of the endometrium. It is possible that endometrial development in the second half of the luteal phase is more likely to be under the influence of local factors, such as the presence or absence of an embryo, than circulating progesterone levels. This is not surprising as the function of the endometrium in the first half of the luteal phase is to prepare itself for the embryo to implant, whereas in the second half of the luteal phase, in the absence of implantation, its main function is to prepare for menstrual shedding of the unused functional layer.

Amongst other factors that may account for the lack of good correlation between endometrial development and salivary progesterone profile in the second half of the luteal phase, one possible explanation may be seen in the results of individual morphometric measurements throughout the luteal phase (Li *et al.* 1988). In general, morphological changes in the first half of the luteal phase, such as the disappearance of mitosis and appearance of secretory vacuoles, are rapid, whereas morphological changes in the second half of the luteal phase, such as the predecidual reaction, are gradual. It may be that the more rapid changes of endometrial morphology in the first half of the luteal phase confer on the measurements a higher degree of precision than the more gradual changes in the second half of the luteal phase. Johannisson *et al.* (1987), who also used morphometric analysis to study the endometrium, similarly found that morphological changes in the human endometrium in the first half of the luteal phase occurred with a higher degree of regularity in comparison to those of the second half of the luteal phase. These explanations may account for the finding in this study that significant association between retarded endometrial development and subnormal progesterone profile was present in the first half of the luteal phase but not in the second half of the luteal phase (Table 1). This implies that endometrial development in the two halves of the luteal phase should be studied separately, otherwise there may be an unduly wide variation in the correlation between endometrial development and progesterone concentration.

Furthermore, half the women with retarded endometrial development, as defined by morphometric analysis, had subnormal salivary progesterone profiles, but the other half had normal profiles which could be due to abnormal response of the endometrium to a normal amount of progesterone, such as a progesterone receptor defect (Cooke & Lambadarios 1974; Keller *et al.* 1979).

Finally, our finding of a better correlation between cumulative salivary progesterone concentration and histological dating with morphometric analysis than with the criteria of Noyes *et al.* (1950) supports the argument that morphometric analysis is better than the criteria of Noyes *et al.* (1950) in the dating of human endometrium (Li *et al.* 1988).

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Minimal/mild endometriosis and infertility. A review

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Introduction

The association between minimal endometriosis and infertility has been a matter for debate for many years.

Kistner (1979) suggested that 30–40% of patients with endometriosis were infertile. Whereas Spangler *et al.* (1971) had found endometriosis in only 6–15% of infertile couples, Mettler & Semm (1979) reported the prevalence in their population of infertile women to be as high as 29%.

It is not difficult to appreciate that moderate or severe disease, where the score according to the Revised American Fertility Society Classification of 1985 (Rev. AFS) is greater than 16, can prevent conception. In these cases the presence of adhesions, fibrosis or significant ovarian disruption by endometriomata provides a mechanical explanation.

Minimal and mild disease (Rev. AFS ≤15) is not associated with significant anatomical distortion. Thus in patients who have no other factor than minimal or mild endometriosis to account for their infertility, it is still unclear how much importance should be attached to this.

Significance of minimal/mild endometriosis

Acosta *et al.* (1973) showed a definite decrease in fertility associated with even mild endometriosis and this was later confirmed by Buttram (1979). However, in recent years doubt has been cast on those findings. Expectant management of endometriosis in patients who are infertile has been compared with the outcome of medical or surgical intervention in both prospective and retrospective studies. The results in terms of pregnancies achieved were similar (Table 1).

These studies raise the possibility that endometriosis of a minimal or mild degree may be an incidental finding and of no importance in the pathogenesis of infertility. If this issue is to be resolved, the prevalence of minimal/mild endometriosis in the general population needs to be determined to enable the fertile and subfertile subgroups within that population to be compared. The logistics of such a task make it impractical at present. Whilst accepting that this debate is yet to be resolved, this review explores some of the recent literature which attempts to explain a causal relation between mild endometriosis and infertility, if such exists.

Peritoneal fluid

A great deal of work has been done to assess various characteristics of peritoneal fluid in patients with endometriosis. The two principal aspects studied have been the prostanoid content of peritoneal fluid and macrophage activity.

Prostanoid content

The prostanoid content of peritoneal fluid in patients with minimal/mild endometriosis has been compared with that in normal fertile women and in women with unexplained infertility. Table 2 summarizes the findings of several groups of workers who have shown greater prostanoid concentrations or content in association with endometriosis when compared with the control group, and those of other workers who were unable to confirm these findings.

These conflicting reports may be related to one of several factors. Timing of the collection of peritoneal fluid samples in relation to the stage of the menstrual cycle varied both between and within studies. Peritoneal fluid volume and cellular and biochemical content, other than prostanoids, alter during the cycle (Koninckx *et al.*

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Table 1. Effectiveness of no treatment compared with medical or surgical treatment on subsequent fertility in women with minimal/mild endometriosis

Study	Treatment	No. of patients: No treatment	No. of patients: Treatment	Pregnancy rate (%): No treatment	Pregnancy rate (%): Treatment
Drake & Grunert (1980)	Methyltestosterone	3	8	100	62*
Seibel *et al.* (1982)	Danazol	28	20	50	30
Hull *et al.* (1987)	Medroxyprogesterone acetate	56	36	55 (cum at 30 months)	71
	Danazol	56	52	55 (cum at 30 months)	46
Thomas & Cooke (1987)	Gestrinone	17	20	24 (cum at 12 months)	25
Garcia & David (1977)	Surgery	17	2	65	100
Shenken & Malinak (1982)	Surgery	18	42	72	76
Portuondo *et al.* (1983)	No treatment	31	—	61 (cum at 18 months)	—

cum, Cumulative pregnancy rate.
*Statistically significant difference between treatment and no treatment.

1980*b*; Donnez *et al.* 1982) and thus the timing of samples needs to be standardized before the results of such studies can be compared. Furthermore, peritoneal fluid for prostanoid measurement needs to be preserved immediately, as any delay will alter the results of assay because of the short half-life of some prostaglandins.

An increased concentration of prostanoids in peritoneal fluid may reflect the presence of peritoneal macrophages (Sun *et al.* 1977; Halme *et*

Table 2. Summary of studies on prostanoid content in peritoneal fluid in women with and without minimal/mild endometriosis

Study	No. of women: Endometriosis	No. of women: No endometriosis	Prostanoid	Stage of cycle sampled
Prostanoid content significantly higher in endometriosis				
Drake *et al.* (1981)	2	9	6-keto-$F_{1\alpha}$, TxB_2	Not stated
Badawy *et al.* (1984*a*)	27*	26	PGE_2, $PGF_{2\alpha}$	Mixed
Koskimies *et al.* (1984)	13	14	6-keto-$F_{1\alpha}$, TxB_2	Mixed
Dawood *et al.* (1984)	16	10	6-keto-$F_{1\alpha}$	Proliferative and luteal
De Leon *et al.* (1986)	26	14	PGE_2, $PGF_{2\alpha}$, 6-keto-$F_{1\alpha}$, TxB_2	Proliferative and luteal
Prostanoid content not significantly higher in endometriosis				
Rock *et al.* (1982)	15	17	PGE_2, $PGF_{2\alpha}$, $PGF_{2\alpha}$ met, TxB_2	Proliferative
Badawy *et al.* (1982)	10	5	PGE_2, $PGF_{2\alpha}$ met	Mixed
Halme *et al.* (1983)	18	26	PGE_2, $PGF_{2\alpha}$	Luteal
Sgarlata *et al* (1983)	7	10	PGE, PGF, $PGF_{2\alpha}$ met, 6-keto-$F_{1\alpha}$, TxB_2	Proliferative
Dawood *et al* (1984)	16*	10	PGE_2, $PGF_{2\alpha}$, TxB_2	Proliferative and luteal
Chacho *et al.* (1986)	32	34	PGE, 6-keto-$F_{1\alpha}$, $PGF_{2\alpha}$ met, TxB_2	Mixed

*Including moderate and severe endometriosis.
$PGF_{2\alpha}$ met = $PGF_{2\alpha}$ metabolite.

al. 1983) or an inflammatory response of the peritoneum to the presence of endometriosis (Herman *et al.* 1979; Drake *et al.* 1981). Alternatively, the endometriotic deposits themselves may be the primary source of prostanoid substances (Moon *et al.* 1981; Ylikorkala & Viinikka 1983).

There are several possible mechanisms by which high levels of prostanoids may contribute to infertility in women with minimal/mild endometriosis. A number of studies have shown that prostanoids have an effect on tubal smooth muscle (Salomy & Goldstein 1978; Omini *et al.* 1978) and thus high levels in peritoneal fluid may alter tubal motility and gamete transport, thereby causing or contributing to infertility (Drake *et al.* 1981).

Prostanoids have also been shown to influence ovarian function in women (Wentz & Jones 1973), both folliculogenesis and corpus luteum function, so that high peritoneal fluid prostanoid levels could prevent conception in women with endometriosis (Badawy *et al.* 1982).

Peritoneal fluid may also have a deleterious effect on sperm function. This may be mediated by prostaglandins. Oak *et al.* (1985) demonstrated reduced motility, velocity and survival of sperm incubated in peritoneal fluid from infertile women when compared with that in peritoneal fluid from fertile controls at the same stage of their cycle, although no distinction could be made between infertile women with or without endometriosis. In contrast, Halme & Hall (1982), using heat-treated peritoneal fluid, were unable to demonstrate an effect on sperm motility nor on penetration of zona-free hamster ova. Furthermore, Stone & Himsl (1986) were unable to demonstrate any difference in sperm motility in peritoneal fluid obtained from women with endometriosis, 2–4 h after artificial insemination, when compared with that in fluid from women with a normal pelvis.

A toxic effect of peritoneal fluid on early embryo development has been demonstrated by Morcos *et al.* (1985). Heat-inactivated peritoneal fluid from women with endometriosis resulted in a greater toxicity to two-cell mouse embryos than did that from infertile women without endometriosis. The toxic component of peritoneal fluid remains to be identified, but the prostaglandin content may be involved.

Macrophage activity

Recently attention has focused on the macrophage population of peritoneal fluid and two possible mechanisms which may account for infertility.

A number of studies (Haney *et al.* 1981, 1983; Halme *et al.* 1982, 1983, 1984; Badawy *et al.* 1984*a*; Chacho *et al.* 1986) have shown elevation of the total macrophage content of peritoneal fluid in patients with mild endometriosis when compared with that in fertile women. In addition, Halme *et al.* (1983, 1984) have shown a greater percentage of activated macrophages in women with mild endometriosis, a more pronounced cyclic alteration in activation and an associated increase in the protease and acid phosphatase content of peritoneal fluid. An increase in complement compounds in peritoneal fluid (Badawy *et al.* 1984*a*) has recently been confirmed by Chacho *et al.* (1986) who also demonstrated that fluid in which peritoneal macrophages had been incubated decreased sperm penetration of zona-free hamster ova, whether the fluid was from women with or without endometriosis, although the former had a higher content of activated macrophages.

From these data, it would seem that if macrophages play a role in the aetiology of infertility associated with mild endometriosis, they do so by virtue of their greater total number and increased level of activation. The release of active substances such as prostanoids, proteases and complement components would be secondary to this and might interfere with conception as discussed above.

Interleukin-1, a protein produced by macrophages, is present in the peritoneal fluid of patients with mild endometriosis but not in fertile controls (Fakih *et al.* 1987). It has also been demonstrated in peritoneal macrophage culture fluid obtained from the same women and shown to be toxic to two-cell mouse embryos (Fakih *et al.* 1987). Interleukin-1 may be an important mediator in the development of infertility associated with minimal or mild endometriosis.

An alternative mechanism, by which activated macrophages may interfere with conception, is sperm phagocytosis. This has been demonstrated *in vitro* (Muscato *et al.* 1982) and was greater for macrophages from women with endometriosis than in disease-free infertile patients and fertile controls.

To summarize, the prostanoid content of peritoneal fluid in women with minimal or mild endometriosis and the source of possibly elevated levels are still matters of debate. Most studies agree, however, that the macrophage content and activation is greater in women with mild endometriosis than in normal women and is associated with the release of active substances which may affect conception in one or more of the following ways: (i) Altered tubal motility; (ii) ovarian dysfunction; (iii) reduced sperm motility or survival; (iv) altered sperm/oocyte interaction; and (v) failure of early embryo development. Sperm phagocytosis by activated macrophages may be an alternative mechanism.

Ovarian function

Anovulation

Soules *et al.* (1976) reported anovulation in 17% of women with endometriosis, 40% having only mild disease. However, the diagnosis was made on the basis of a scoring system rather than by luteal phase progesterone assay or ultrasound

Dmowski *et al.* (1976) reported anovulation in association with endometriosis and confirmed this in a later study (Dmowski *et al.* 1986) in which 9% of a total of 450 women with endometriosis were anovulatory. In a separate, prospective study (Dmowski *et al.* 1986) 21% of patients with mild disease were anovulatory.

Why anovulation should coexist with mild degrees of endometriosis is unclear. It may be that a defect in ovarian function is the primary disorder and that endometriosis is a consequence of this. Alternatively, prostaglandins or other substances produced by endometriotic tissue have an effect on ovarian function and may cause anovulation.

Luteal phase defects

More subtle forms of ovarian dysfunction have also been described. Hargrove & Abraham (1980) showed deficient luteal phases in women with endometriosis by measurement of ovarian steroids in three pooled blood samples obtained in the mid-luteal phase. Concentrations of oestradiol were higher than normal, whilst concentrations of progesterone were low.

Brosens *et al.* (1978) demonstrated a delayed rise in progesterone concentrations after ovulation and a shortening of the luteal phase in women with endometriosis. Cheeseman *et al.* (1982, 1983) confirmed the delay in progesterone secretion and also demonstrated biphasic pre-ovulatory luteinizing hormone (LH) peaks in a significant proportion of women with endometriosis. The duration of the luteal phase, when timed from the second LH peak, was shorter than in women without endometriosis. It was suggested that, as the rise in progesterone followed the second LH peak, it was more appropriate to estimate the duration of the luteal phase in this way, thus arriving at a more accurate representation of the 'functional luteal phase' (Cheeseman *et al.* 1983). Biphasic LH peaks and a delay in progesterone secretion have been confirmed in this department (Vaughan Williams *et al.* 1986).

Another possible contributory factor, suggested by Ronnberg *et al.* (1984), is a reduction in the concentration of LH receptors, both in follicular and luteal tissue, in women with endometriosis when compared with those without the condition These authors suggested that the follicle would therefore be less sensitive to LH, thus accounting for failure of ovulation and defective corpus luteum formation.

Failure of luteolysis as a factor in the infertility of women with mild endometriosis has been proposed by Ayers *et al.* (1987), who found raised progesterone levels in the follicular phase of the cycle and suggested that a persistent corpus luteum continued to produce progesterone well into the subsequent cycle and possibly caused premature luteinization of the current dominant follicle.

Defective luteal function in patients with mild endometriosis has not been confirmed in studies using the relatively insensitive indices of endometrial histology (Pittaway *et al.* 1983) and a single measurement of progesterone in the mid-luteal phase (Radwanska & Dmowski 1982).

Luteinized unruptured follicle (LUF) syndrome

Infertility associated with endometriosis has also been attributed to luteinization of an unruptured follicle (LUF syndrome), which has been reported in 77% of women with mild endometriosis (Brosens *et al.* 1978). But subsequent studies have not been entirely supportive of these original data. Marik & Hulka (1978), Dmowski *et al.* (1980) and Dhont *et al.* (1984) all showed an association between endometriosis and the LUF syndrome but not of the same level as reported by Brosens *et al.* (1978). Dmowski *et al.* (1986) demonstrated LUF in only 34% of women with endometriosis.

These conflicting results may be due, in part, to the different diagnostic criteria used in these studies. These include the absence of an ovulatory stigma on the ovaries at laparoscopy (Marik & Hulka 1978; Brosens *et al.* 1978), absence of the postovulatory rise in oestradiol and progesterone concentrations in peritoneal fluid (Koninckx *et al.* 1980*a*; Dhont *et al.* 1984) and lack of follicular rupture demonstrated by means of serial follicular ultrasonography (Coulam *et al.* 1982; Liukkonen *et al.* 1984).

Dmowski *et al.* (1980) questioned the reliability of the first of the described diagnostic methods, and Dhont *et al.* (1984) the second. Serial ultrasonography is probably the most appropriate method for the diagnosis of LUF, being a rapid, relatively inexpensive and, of particular importance, a non-invasive procedure which can be repeated as often as required. Some reports have highlighted discrepancies between the findings of this and other diagnostic methods (Janssen-Caspers *et al.* 1986), demonstrating the need for further studies to elucidate the role of LUF in the aetiology of infertility associated with endometriosis.

Thus, a variety of defects in ovarian function, from anovulation to LUF and including many subtle abnormalities of the pituitary ovarian axis, may coexist with endometriosis, thereby contributing to infertility. Whether these abnormalities are secondary to endometriosis or are responsible for promoting the disease in some women remains unclear.

Autoimmune phenomena

Several workers have explored the possibility of an autoimmune aetiology for infertility associated with endometriosis. Weed & Arquembourg (1980) were the first to detect an antibody to endometrial tissue in patients with endometriosis. Their findings have since been confirmed (Mathur *et al.* 1982; Badawy *et al.* 1984*b*) but the antigen has not been identified. However, Joshi *et al.* (1986) have been unable to demonstrate the presence of endometrial antibodies. In addition, a notable proportion of patients with endometriosis have high serum levels of other autoantibodies of IgG and IgM classes (Gleicher *et al.* 1987) which suggests the presence of polyclonal B-cell activity, a characteristic of other autoimmune diseases. Together with its female preponderance, familial tendency, multi-organ involvement and association with other autoimmune diseases (Gleicher *et al.* 1987), these findings indicate that the autoimmune aspect of infertility associated with endometriosis warrants further investigation.

Conclusion

The role of minimal or mild endometriosis in the aetiology of infertility remains unclear but an increased prostanoid content and macrophage activity in peritoneal fluid may exert an effect by a variety of mechanisms, including altered tubal motility, sperm function and early embryo wastage. Ovarian function may be altered in a variety of ways, including many subtle abnormalities only detectable by detailed investigation. Autoimmune phenomena may also be contributory. The profusion of data is confusing and it becomes increasingly clear that many of these factors may coexist and that no single abnormality may account for infertility in women with mild endometriosis. The multiplicity of these abnormalities suggests that the development of endometriosis may be a common consequence of these, rather than their cause, and as such, treatment of the disease will not necessarily improve fertility.

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Screening donors for sexually transmitted disease in donor insemination clinics in the UK. A survey

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Summary. A survey conducted amongst the 40 donor insemination centres in the UK registered by the Royal College of Obstetricians and Gynaecologists (RCOG) showed that most of the clinics had no structured policy for control of common (non-HIV) sexually transmitted diseases within their programmes.

Donor insemination (DI) is an established treatment for male infertility and requests for this treatment are increasing. There were 1751 births resulting from DI in 1985 that were reported to the Royal College of Obstetricians and Gynaecologists (UK) Fertility Subcommittee (RCOG 1987). Reports of maternal infection resulting from the use of contaminated donor semen by pathogens such as human immunodeficiency virus (HIV) (Stewart *et al.* 1985) have been a cause of considerable concern. Recently, the American Fertility Society published stringent guidelines to prevent the spread of sexually transmitted disease (STD) by this procedure (AFS 1986). They concluded that careful screening of potential donors together with routine surveillance of their health were important methods of reducing this risk In the UK, however, definitive recommendations only exist for the control of HIV infection (DHSS 1986).

We undertook a survey of registered clinics in the UK to determine current screening practices for excluding STD in semen donors.

Materials and methods

To review current screening practices in DI clinics, a questionnaire was designed which covered the following aspects in detail: donor recruitment and exclusion policies, clinical examinations, urethral and serological tests, microbiological analysis of the semen, storage of semen, tests on recipients, and maintenance of records pertaining to altered pregnancy outcome secondary to infection. This was circulated in October and November 1987 with an explanatory letter to all physicians in charge of the 40 DI centres which were registered with the RCOG Fertility Subcommittee.

Results

Thirty-seven replies from the 40 centres that were contacted were received. One centre had suspended recruitment because of inadequate facilities for storage, four centres obtained straws from other clinics which were registered with the RCOG. We therefore report on the information from only 32 centres including our own. The results obtained from the questionnaire are reported in Table 1.

Semen cultures rather than urethral tests were used by most centres to detect genital infections, and of those that did, many tested for non-STD

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Table 1. Summary questionnaire submitted to UK donor insemination clinics

Questions	Per cent positive (32 centres)
Selection of donors	
1. How do you recruit donors?	
Previously fertile men	31
Advertise in press (national)	10
Advertise in university press	41
University posters	58
Word of mouth	90
2 What demographic group constitutes the majority of your donors?	
Students	75
Married men alone	25
3. Are your donors paid?	84
4 Do you liaise with a genitourinary medicine clinic?	68
Details of donor history obtained	
1. Number of sexual partners in the past 6 months?	47
2. Regular sexual partner?	65
3. Previous history of genital infections?*	84
Examination and investigations	
1. Do you perform a genital examination?	31
2. Do you perform urethral tests for	
Leucocytes (Gram-stained smear)	6
Chlamydia trachomatis	9
Neisseria gonorrhoeae	9
Mycoplasma/Ureaplasma	3
Trichomonas vaginalis	9
3 Do you perform serological tests for	
Chlamydia trachomatis	53
Treponema pallidum	90
Hepatitis B virus	97
Human immunodeficiency virus	100
Cytomegalovirus	28
4. Do you perform regular tests on donors?*	90
5 Do you perform semen cultures?	
Anaerobic bacteria	69
Aerobic bacteria	60
Chlamydia	40
Ureaplasma/Mycoplasma	34
6. Do you test for leucocytes in semen?*	97
Use of semen for insemination	
1. Do you use frozen semen exclusively?	77
2. Do you use fresh semen exclusively?	6
3. Do you use both?	16
4. Do you cryopreserve semen for 3 months and test the donor prior to its use?	93
Recipients	
1 Do you perform any genital test?	31
2. Do you perform any serological tests?	90
3. Do you match CMV serological status of donors and recipients?	9
Donor exclusions	
1. Do you exclude men who have had a previous STD?	
Gonococcus	81
Non-specific urethritis	69
Herpes	81
Warts	60
Syphilis	84
2. Do you exclude men who have leucocytes in semen?	41
3 Do you keep a record of altered pregnancy outcome which may be the result of infection following DI?	84

*See text for details.

organisms, predominantly aerobic or anaerobic bacteria. Phase contrast microscopy was the preferred method of demonstrating leucocytes, and in the centres that stated a significant level, estimates ranged from 1 to 30×10^6/ml.

Most centres excluded men if they had any previous history of STD. Infections such as gonorrhoea, non-gonococcal urethritis, syphilis, genital herpes and warts were always considered to be very important but many clinics failed to ask specifically about a history of viral infections. Overall, centres estimated that between 1% and 50% of potential donors were rejected because they posed a significant risk of infection.

Once accepted on to a programme, only 24% of the responding centres regularly enquired as to whether the donor had had a change of sexual partner since the last clinic visit. Most men were subject to regular tests, but this was limited in most cases to screening for HIV antibodies every 3 months in accordance with DHSS guidelines.

Discussion

This survey demonstrates that, at present, there is no systematic, comprehensive approach by DI clinics in the UK to prevent the spread of common sexually transmissible pathogens to recipients although there is some awareness of the problem.

There is evidence that this risk is likely to be significant but we do not at present know how often serious infections are transmitted to recipients as no prospective microbiological studies have been published. Monteiro *et al.* (1987) detected urethral infection with STD pathogens in one-third of 36 potential semen donors who were examined. In addition, Tjiam *et al.* (1987) screened 237 semen donors from 10 DI centres and found 47% to be infected. A variety of organisms were isolated in this study including *Chlamydia trachomatis* (6·3%), *Mycoplasma hominis* (4·6%), *Ureaplasma urealyticum* (35·9%), and cytomegalovirus (0·4%). Direct evidence of transmission of infection by DI is, however, anecdotal. Stewart *et al.* (1985) investigated HIV transmission and showed that four of eight recipients who were inseminated with semen from an infected man subsequently seroconverted. Interestingly, the recipients who were uninfected were inseminated with semen that was cryopreserved for a period of >4 months which suggests that this procedure may inactivate the virus. There have been other case reports of transmitted infections including *Ureaplasma urealyticum* (Barwin 1984), *Neisseria gonorrhoeae* (Fiumara 1972) and *Chlamydia trachomatis* (Nagel *et al.* 1986). Two excellent reviews by Greenblatt *et al.* (1986) and Mascola & Guinan (1986) have highlighted the possible serious sequelae of such infections in the woman which may then be transmitted to her sexual partner and fetus. Complications in the woman include pelvic inflammatory disease, chorioamnionitis and premature rupture of membranes, and fetal complications include congenital abnormalities, low birthweight and neonatal sepsis.

There are several problems in designing a screening strategy for sexually transmitted diseases in men who are willing to be semen donors. Recruitment of suitable men remains a major problem and many centres encourage attendance by a policy of payment either of expenses or as a fee. In our survey we did not distinguish between the payments given to donors as a fee or for expenses. However, blood transfusion centres in the USA have found that payment may attract some individuals who are predominantly financially motivated and who may also be involved in high-risk behaviour which may or may not be revealed at interview because of fear of exclusion. This pattern may exist whenever a significant payment is made. Other policies are also questionable. We note that clinics exclude men who have any history of STD and some perhaps hope to reduce the risk of infection by recruiting married men alone. This approach is illogical as several genital bacterial infections are completely curable and many otherwise suitable men would be excluded. Furthermore, married men are not immune to genital infections and must be screened prospectively.

Very few centres ask for details of genital tract disease or perform a genital examination. We find information obtained in this way useful in assessing the current and future risk of acquiring STD and in facilitating the diagnoses of active genital infections and conditions for which there are currently no routine laboratory tests, such as human papillomavirus (HPV) infection. Urethral tests can also be taken during an examination, a practice which is well established in UK genitourinary departments. These tests are not used by most centres but some appear to use semen cultures as an alternative; however, there are few data available on the reliability of conventional microbiological tests on semen (Barratt *et al.* 1988). Serological tests also appear to be widely used but are only useful for certain infections. In particular, serological studies for *Chlamydia trachomatis* are of no value in the diagnosis of uncomplicated genital infection (Oriel & Ridgway 1982).

Considerable concern has been expressed in the USA regarding primary cytomegalovirus (CMV) infection in recipients. Serological screening for CMV is performed in only nine UK centres. Recently Hammitt *et al.* (1988) consistently recovered biologically active antigen in several specimens of fresh and cryopreserved semen from one of four CMV-seropositive donors. Reinfection by different subtypes of CMV has been demonstrated also in seropositive renal allograph recipients who are immunocompromised. This mechanism remains a theoretical possibility in healthy individuals. The American Fertility Society (AFS) currently recommends that all donors be screened and only CMV-negative donors matched to CMV-negative recipients. They also suggest that centres consider excluding all CMV-positive donors, but we do not feel that there is enough evidence to justify this. Adoption of this latter policy would also exclude approximately 40% of the donors in our department (Chauhan *et al.* 1989). Although in the UK, studies on congenital infection in normal conceptions have been reassuring, only 0·03% of all livebirths being seriously handicapped by this infection (Best 1987), research on rates of transmission and sequelae of infections are urgently needed in women undergoing DI.

The significance of seminal leucocytes as an indicator of underlying genital infection is controversial (Barratt *et al.* 1988). Overall, 93% of the centres estimate seminal leucocytes, usually by phase contrast microscopy. Interestingly, El-Demiry *et al.* (1986*a*, *b*), using monoclonal antibodies, demonstrated that the semen of fertile men contained significantly more white blood cells than semen of infertile men, and the number of leucocytes was not related to the isolation of micro-organisms in a semen culture. The function and significance of these leucocytes require further research.

We were surprised that five centres have continued to use fresh semen despite the DHSS guidelines to control HIV infection. With recent evidence suggesting that frozen semen is almost as efficacious as fresh semen (Hammond *et al.* 1986) there is no rationale for use of the latter. In the UK, the seroprevalence of HIV outside high-risk groups is low (CDSC 1988). Indeed Bromwich *et al.* (1986) showed that none of the 233 donors attending the British Pregnancy Advisory Service was infected, but continued vigilance is clearly necessary as spread occurs outside the high-risk groups into the heterosexual population.

There is no doubt that consumer demand for DI is continuing. The report of transmission of HIV could have altered this, but sensible changes in policy will have restored patient confidence. The problem of preventing transmission of common STD pathogens now needs to be addressed. This could be accomplished in different ways. First, either the men or their semen could be examined and screened at each donation; second, antimicrobial agents could be added to semen to neutralize any pathogens; and third, vaccines could be administered to protect recipients against serious infections. However, there are problems with each strategy either because of inconvenience, incomplete data, unsuitable therapeutic agents or expense. We have recently proposed a protocol for screening potential donors based on the recruitment of 192 potential donors (Chauhan *et al.* 1988). This uses a synthesis of strategies which includes the AFS guidelines. The policy we feel is practicable and achieves a balance between absolute prevention, which would exclude most men, and adequate infection control (see Table 2). We have found a close liaison with a genitourinary clinic to be extremely useful and the procedures highly acceptable to donors after appropriate counselling.

In conclusion, we propose the establishment of multicentre studies to investigate the prevalence of transmitted disease and its complications in recipients, particularly CMV infection, and the most efficient methods of screening donors for STD. It is fortunate that some centres already perform tests on recipients and most have records of altered pregnancy outcome relating to infection following DI. These results could be used in a future survey. Perhaps the RCOG should co-ordinate such studies and, like the AFS, provide national guidelines for the control of common STD pathogens in DI clinics. Adoption of such policies would ensure the health of recipients and the future of such programmes in the UK which have provided a successful treatment for male infertility

Table 2. Recommendations for prospective screening of semen donors in the UK to exclude sexually transmitted infections

Initial screening

1 Precounselling
    Exclude all men in high-risk groups for HIV (DHSS 1986)
2. History
    Current genital symptoms
    Previous history of STD
    Sexual history (number of sexual partners in previous 6 months)
3. Genital examination
    Genital ulcer disease
    Genital warts
    Urethral discharge
4. Urethral tests (men should hold their urine for 4 h preceding these tests)
    Gram-stained smear
    Neisseria gonorrhoeae
    Chlamydia trachomatis
    Ureaplasma urealyticum
    Mycoplasma hominis
    Trichomonas vaginalis
5. Serological tests
    Human immunodeficiency virus antibody
    Treponema pallidum (VDRL, TPHA)
    Cytomegalovirus antibody
    Hepatitis B virus (HbsAg, antiHbc)
6. Exclude all men who have a history of evidence of any viral STD (including hepatitis B virus); treat those men who have STD; arrange follow-up and contact tracing; reconsider as donors those men who have microbiologically cured bacterial STD and a stable sexual relationship
7 Obtain adequate specimens of semen
8. Use CMV-seronegative men as universal donors; CMV-seropositive donors should donate to CMV-seropositive recipients only
9. Consider vaccinating recipients for hepatitis B virus (if seronegative) before DI procedures

Follow-up of regular donors

1. Rescreen donors for common STD pathogens if clinically indicated, such as a change of sexual partner or the development of genital symptoms, a relevant history should be sought at each donation, alternatively, men could be screened every 3–6 months
2. Use cryopreserved semen only, each batch should be quarantined for a minimum of 3 months and the donor seronegative for HIV after this time (DHSS 1986)

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The aetiology of vaginal bleeding in children. A 20-year review

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Summary. The cause of vaginal bleeding in girls of 10 years and under is reviewed. Of the 52 patients seen, in 28 (54%) bleeding was caused by a local lesion and 11 (21%) of these had malignant genital tumours. Eleven (21%) children presented with some form of precocious puberty, and in 13 (25%) patients no cause could be found.

Vaginal bleeding in girls is a rare but alarming symptom, and may be caused by serious underlying pathology. All children should be investigated and examined under anaesthesia, including vaginoscopy.

This study is a review of girls aged 10 years and under who presented to the Chelsea Hospital for Women with vaginal bleeding during the past 20 years. The age of 10 was chosen as the upper limit for this study because after that time menstruation may be physiological (Dewhurst 1971; Reiter 1972). The Chelsea Hospital for Women is mainly a secondary referral centre and many girls in this series had been seen initially in other gynaecological or paediatric units; therefore this series may not represent a true cross-section of the disease spectrum.

Patients and methods

The case notes of all patients, 10 years of age and under, who presented with vaginal bleeding between 1966 and 1986 were reviewed retrospectively. Historical factors relevant to determining the aetiology of the bleeding such as oral contraceptive ingestion, duration and cyclical nature of the bleeding were noted. Clinical examination and the presence or absence of secondary sexual characteristics were recorded. All patients were examined under anaesthesia. Vaginoscopy was performed in small infants using a cystoscope or hysteroscope; in larger infants direct inspection of the vagina and cervix was achieved by passing a paediatric laryngoscope. The final diagnosis, subsequent management and follow-up were also noted.

Results

Overall, 52 girls were seen during the study period; their age range was 7 months to 10 years (Table 1) (mean 4·75 years). The aetiology of the vaginal bleeding is shown in Table 2. In 28 girls (54%) bleeding was from a local lesion and in 11 of them (21%) bleeding was due to a malignant genital tract tumour. Eight were rhabdomyosarcomas (botryoid sarcoma); two were clear-cell vaginal adenocarcinomas and one was an endodermal sinus tumour.

Three of these 11 children with tumour died during the study period. The first was a 19-month-old Egyptian girl who had vaginal bleeding for over a year before being seen. At operation she had a large inoperable clear-cell adenocarcinoma which failed to respond to radiotherapy. The second was a 2-year-old girl with a rhabdomyosarcoma who presented with a 6-month history of blood-stained discharge. A biopsy at another hospital was reported as showing inflammatory changes only. She received high-dose chemotherapy, but at subsequent laparotomy was found to have an inoperable

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Table 1. Age at presentation

Age (years)	No. of girls
0–1	6
1–2	7
2–3	4
3–4	2
4–5	8
5–6	5
6–7	3
7–8	4
8–9	2
9–10	5
10	6

tumour. The third was a 16-month-old girl who presented with a 1-week history of vaginal bleeding, but despite an anterior exenteration for a yolk sac tumour, radiotherapy and chemotherapy, she died. The other eight girls are alive and disease free at follow-up, 5–18 years later.

In five children vaginal bleeding was secondary to a vulval lesion. This was lichen sclerosis in two, vulval warts in another two, and a cavernous haemangioma in the fifth. In a further five children vaginal bleeding was secondary to urethral prolapse. Four girls presented with trauma causing vaginal bleeding; three of these followed various types of falls, and the last had a ruptured hymen possibly linked to a previous foreign body. In three children bleeding was due to vulvo-vaginitis.

Vaginal bleeding was caused by some form of precocious puberty in 11 children. Precocious puberty was constitutional in two girls, and in three others pseudo-precocious puberty was associated with a granulosa cell feminizing tumour. In the six remaining girls cyclical bleeding was the only sign of precocious puberty and so a diagnosis of premature menarche was made. None of the children had evidence of McCune-Albright syndrome.

In the remaining 13 girls (25%) no clear cause could be found.

Discussion

Where a definite diagnosis was made, the commonest aetiological causes were malignant genital tumours ($n = 11$) and precocious puberty ($n = 11$). The high frequency of malignant tumours may reflect the secondary referral role of the Chelsea Hospital for Women. Most of the tumours were rhabdomyosarcomas which are mixed mesodermal tumours. They may be found at any age during childhood, but are more common in children under 3 years of age (Dewhurst 1983). The vagina is the commonest site of the tumour in the young, but the cervix may also be involved. The appearance of the tumour may vary but classically it resembles a bunch of grapes. The tumour usually presents with vaginal bleeding which may be accompanied by the passage of a piece of tumour tissue. Sometimes the tumour may be visible at the vaginal orifice, but examination under anaesthesia and biopsy is usually necessary to make the diagnosis. Occasionally histological diagnosis may be difficult due to the pleomorphism of the tumour. Histological misdiagnosis may result in delayed treatment, as unfortunately occurred in the 2-year-old girl who died. Early cases in the series were treated surgically, but the more recent ones have been treated with chemotherapy.

Two children in the present series presented with clear-cell adenocarcinomas. Neither of them had been exposed to diethylstilboestrol (DES) *in utero*. The association between these tumours and DES was first described by Herbst & Scully (1970). The risk of developing clear-cell adenocarcinoma after exposure to DES has been estimated to be 0·14–1·4/1000 of DES-exposed females (Emens 1984). Both girls were treated with extended hysterectomy, vaginectomy and radiotherapy. During the study period a 13-year-old girl who had been exposed to DES *in utero* did present with a clear-cell adenocarcinoma. She was successfully treated with radiotherapy (Dewhurst & Ferreira 1980). The exact place of chemotherapy in the management of these tumours is as yet unknown.

Endodermal sinus tumours of the vagina are the rarest vaginal tumours in this age group, and are also some of the most malignant. Only one

Table 2. Aetiology of vaginal bleeding

	Number	(%)
Genital tumours	11	(21)
Precocious puberty	11	(21)
Vulval lesions	5	(10)
Urethral prolapse	5	(10)
Trauma	4	(8)
Vulvo-vaginitis	3	(6)
Unknown aetiology	13	(25)
Total	52	(100)

girl was diagnosed as having this tumour and she was treated surgically (Dewhurst & Ferreira 1981).

Precocious puberty is defined as the appearance of physical signs of secondary sexual development before the age of 8 years or of menstruation before the age of 10 years (Dewhurst 1971). Pseudoprecocious puberty may be caused by feminizing granulosa cell ovarian tumours. Classically, bleeding presents early and unlike other causes of precocious puberty the bone age is not in advance of chronological age (Dewhurst 1980). The diagnosis is made by detection of a mass, and endocrine investigations show high oestrogen levels. In most of our girls with precocious puberty, cyclical bleeding occurred without other signs of secondary sexual development. This is classified as premature menarche and is thought to be due to unusual sensitivity to very low levels of circulating oestrogen (Heller *et al.* 1983). Hormone assays are normal and the bone age corresponds with the chronological age. No treatment is required once a more serious cause has been excluded. The bleeding usually stops by 10 years of age and starts again after the appearance of the other signs of secondary sexual development. Subsequent development of such patients appears to be normal, as is their future fertility (Murran *et al.* 1983). Exogenous oestrogen ingestion in the form of the oral contraceptive pill or in the diet should be excluded (Comas 1982; Schoental 1983). Two girls had constitutional precocious puberty which is attributed to spontaneous initiation of hypothalamic and pituitary activity. It presents with cyclical bleeding in association with other signs of secondary sexual development. Both girls in this series had radiographic signs of advanced bone age and breast development before menstruation.

A variety of vulval lesions may affect the young child, but few cause vaginal bleeding. Lichen sclerosis was diagnosed in two children. This disorder is similar to the condition which affects postmenopausal women and it usually disappears at puberty (Dewhurst 1984). Genital warts may cause bleeding occasionally and their presence may suggest infection by a parent or sexual molestation. This was not evident in either of our children.

Urethral prolapse is a relatively common mistaken cause of 'vaginal' bleeding in children and was found in 10% of our series. It occurs most often at between 5 and 9 years of age (Editorial 1979). It is more common in children of negroid extraction (Klaus & Stein 1973) Urethral prolapse may be related to low levels of oestrogens and presents with a circular prolapse at the external urethral orifice. Occasionally the prolapse may be difficult to distinguish from a genital tumour. If the prolapse is large it is best treated by surgical excision of the necrotic mucosa.

If bleeding is associated with trauma, examination under anaesthesia is necessary because lacerations of the vulva may appear relatively minor on external inspection and external blood loss may be deceptively small in the presence of significant vaginal haematoma (Heller *et al.* 1978). Although no cases of trauma associated with a foreign body were found in this study it has been reported to cause up to 30% of vaginal bleeding in children (David *et al* 1984).

Vaginitis and vulvo-vaginitis, although quite common, rarely cause vaginal bleeding. It occurred in only 3 (6%) children in this series.

In all the 52 children seen with vaginal bleeding during the study period no case of sexual abuse was confirmed. However, it may be that these unfortunate children tend not to be referred to secondary centres.

Conclusion

Vaginal bleeding in children is a rare occurrence, and a serious underlying cause should always be excluded. Examination under anaesthesia and vaginoscopy are mandatory in all cases. Few series have been published, and the incidence of various aetiologies differs widely between studies. The numbers of patients seen by any clinician are small, so it is preferable that the children be referred to specialized centres.

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Radiation exposure of the ovaries during hysterosalpingography. Is radionuclide hysterosalpingography justified?

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Summary. Before the introduction of radionuclide hysterosalpingography in our clinic we measured the ovarian radiation exposure during hysterosalpingography (HSG) with fluoroscopy. Radiation dosage varied from 0·33 to 3·74 mGy and increased with both the number of spot films taken and the duration of fluoroscopic exposure. Compared with the conventional HSG, radionuclide HSG delivers an approximately 25 times higher dose of ionizing radiation to the ovaries.

Recently, McCalley *et al.* (1985) described radionuclide hysterosalpingography (HSG) for the assessment of fallopian tube patency, using the technique introduced by Venter & Iturralde (Venter & Iturralde 1979; Iturralde & Venter 1981). Technetium-99m (^{99m}TC)-labelled human serum albumin microspheres, suspended in 1 ml of normal saline, were applied directly on to the cervical mucosa using a syringe with a blunt needle. Images were obtained 15 to 60 min after application of the labelled microspheres. A fallopian tube was considered patent if a relatively intense focus of radioactivity was imaged in the area of the adnexa. Radionuclide HSG offers a new method for the study of tubal physiology. In patients sensitive to iodine, it might be used as an alternative for routine HSG.

The amount of radiation to the ovaries was stated to be in the median range for a standard HSG (McCalley *et al.* 1985). Radionuclide HSG resulted in a total absorbed dose of 0·76 mGy/MBq (2·8 rad/mCi) to each ovary Iturralde & Venter (1981) measured radioactivity levels in removed organs and tissues after deposition of 370 MBq (10 mCi) (^{99m}TC) in the posterior fornix. High radioactivity levels were found in the adnexa. The National Council on Radiation Protection and Measurements (1977) reported absorbed doses by the ovaries from X-ray HSG of 67 mGy not including the dose due to fluoroscopy. McCalley *et al.* (1985) calculated a dose to the ovaries from X-ray HSG of 2·25 mGy for each spot film plus an additional 6 mGy for each minute of fluoroscopy.

Preceding the introduction of radionuclide HSG in our clinic we measured the radiation exposure of the ovaries during HSG with fluoroscopy

Patients and methods

All 25 patients included in this study were investigated by HSG for infertility by the same physician using a Schultze hysterosalpingograph, and the same X-ray machine (Siemens, pantoskop 3), with high voltage kept constant at 85 kV. The tube/film distance remained as constant as possible.

Thermoluminescent crystals (TLD principle) carried by a small container were attached to the conus of the hysterosalpingograph (Fig. 1) and directed towards the X-ray tube. The thermo-

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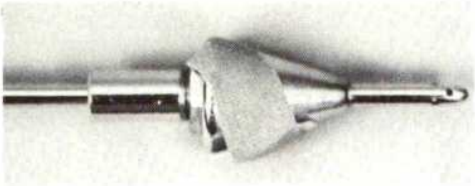

Fig. 1. Thermoluminescent detector container attached to the hysterosalpingograph conus.

luminescent detectors were measured by the radiological service of TNO, Arnhem, Netherlands. HSG was performed using fluoroscopy intermittently with minimum exposure time.

Results

Table 1 shows data from this study. The average radiation dose for diagnostic HSG was 1·08 mGy and included radiation during fluoroscopy and radiation with two ($n = 12$) or three ($n = 13$) films. The radiation dose increased with both the number of spot films taken and the duration of fluoroscopic exposure. The number of films and the fluoroscopic time were associated; e.g. fluoroscopic radiation for >25 s was needed in two patients with two films and in eight patients with three films.

Discussion

Muller (1954), who received the Nobel Prize in Physiology and Medicine in 1946 for his discovery of the production of mutations by X-rays, stated in regard to irradiation of the gonads that no dose was small enough to be devoid of mutagenic effect. HSG is used as a diagnostic procedure to assess the infertile woman, and since many will eventually conceive, the radiation exposure of their ovaries is an important consideration.

Table 1. Radiation exposure during hysterosalpingography with fluoroscopy in 25 women

	No. of women	Average radiation dose (mGy)
All procedures	25	1·08
Two spot films	12	0·70
Three spot films	13	1·32
Fluoroscopic exposure time*		
≤25 s	14	0·67
>25 s	11	1·59

*Average fluoroscopic time for 25 procedures was 24 s.
1 mGy = 100 mrad.

Radionuclide HSG delivers a total dose of 0·76 mGy/MBq to each ovary (McCalley *et al.* 1985). We measured the amount of radiation exposure in the near vicinity of the ovaries and found doses between 0·33 and 3·74 mGy with an average of 1·08 mGy in 25 women. These findings confirm earlier reports (Shirley 1971; Sheikh & Yussman 1976; Freedman *et al.* 1987) of radiation exposure during HSG. Numerous investigators have attempted to improve the diagnostic accuracy of HSG while decreasing the amount of radiation used. Freedman *et al.* (1987), using electronic fluorography to perform HSG, measured significantly decreased doses of ionizing radiation to the ovaries.

Radionuclide HSG could add to our knowledge of tubal physiology, but is certainly not an essentially innocuous technique. It remains to be seen if the added information warrants an approximately 25 times higher radiation exposure of the ovaries.

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Infection with *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in women with lower abdominal pain admitted to a gynaecology unit

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Summary. One hundred and sixty-five women admitted to a gynaecology unit with lower abdominal pain were screened for infection with *Neisseria gonorrhoeae* and *Chlamydia trachomatis* by members of a department of genitourinary medicine. *C. trachomatis* alone was detected in 21 patients. *N. gonorrhoeae* alone was isolated from five patients, and dual infection was present in six patients, giving a total of 32 (19%) patients in whom a sexually transmitted disease (STD) was diagnosed. The combination of an endocervical swab placed in Amies transport medium for gonococcal isolation and an endocervical slide for immunofluorescent detection of chlamydiae proved to be a simple and accurate method of screening for STD. As a result of contact tracing, 16 sexual partners of women in whom STD was detected were examined. Three cases of gonococcal and nine cases of non-gonococcal urethritis were diagnosed. None of the sexual partners had symptoms suggestive of genitourinary infection.

Lower abdominal pain in young women is a common cause of admission to gynaecology units. The differential diagnosis includes pelvic inflammatory disease (PID), ectopic pregnancy, abortion and complications of ovarian cysts (Beard *et al.* 1986). Cysts and the complications of pregnancy can usually be excluded by the combination of an ultrasound examination and estimation of the plasma level of the beta subunit of human chorionic gonadotrophin (β-hCG) (Kadar *et al.* 1981). The management of possible PID may be more haphazard, particularly with regard to diagnosing infection by *Chlamydia trachomatis* and *Neisseria gonorrhoeae,* both of which are important causes of salpingitis (Mardh 1980). Diagnostic methods that would be employed in genitourinary medicine departments such as direct plating of material on to modified New York City (MNYC) medium which is selective for gonococcal isolation (Young 1978), and inoculation of McCoy cells for chlamydial culture (Evans & Woodland 1983) may not be readily available, and undue reliance may be placed on a less sensitive method such as a high vaginal swab (Battacharyya *et al.* 1974).

The aim of this study was to develop liaison between the departments of genitourinary medicine and gynaecology at the Royal Infirmary of Edinburgh in the management of women suspected of PID, both by improving diagnostic methods and also by demonstrating the value of contact tracing and examination of sexual partners.

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Patients and methods

The study included 165 patients investigated between July 1985 and August 1986 whose prime complaint was of lower abdominal pain when admitted as emergencies to the Royal Infirmary of Edinburgh under the care of the gynaecologists. Routine investigation consisted usually of a white blood count, ESR, midstream urine specimen, dry high vaginal swab, estimation of β-hCG and an ultrasound examination. Laparoscopy was performed on 50 patients with more severe symptoms or in whom there was continuing diagnostic uncertainty. Patients thought likely to have PID on the basis of standard criteria were referred to two of the authors (either G.R.S. or C.T.) for detailed bacteriological screening. Patients who had received antimicrobial therapy within the previous 2 weeks were excluded.

The system was designed to work along the following lines. A minority of the patients were admitted during office hours, and these patients were screened within 3 h of admission. A more typical patient with lower abdominal pain was admitted as an emergency during the evening and overnight. If the presumptive diagnosis was PID, the gynaecology registrar or senior registrar decided whether immediate antimicrobial therapy was necessary. Patients given immediate therapy were excluded from further study. If the patient's condition was judged sufficiently mild, she was simply observed overnight and given analgesia if appropriate. The next morning, either G.R.S. or C.T. contacted the overnight waiting team for a list of such patients. Specimens for bacterial culture were obtained in the gynaecology wards.

The following specimens were obtained using cotton-wool-tipped applicator sticks. Urethral, cervical and rectal material was plated directly on to MNYC medium (Young 1978). Within 30 min the plates were placed in an incubator in a carbon dioxide enriched (10%) atmosphere at 37°C. After 24 h incubation, the presence of oxidase-positive Gram-negative cocci was sought. *N. gonorrhoeae* was identified by sugar utilization and coagglutination (Young & McMillan 1982). An endocervical swab was also placed in Amies transport medium and transported to the laboratory within 4 h. Material from the swab was then plated on to MNYC medium, and *N. gonorrhoeae* was identified.

For chlamydial detection, an endocervical swab was expressed into 1 ml of 2SP transport medium which was placed in a freezer at −70°C within 30 min. Care was taken to ensure that the cervix had been cleaned of vaginal exudate before material was obtained. Isolation was attempted in McCoy cells which were incubated in growth medium for 72 h. Cells were then stained with iodine, and *C. trachomatis* was considered to be present if characteristic intracytoplasmic inclusions were seen (Evans & Woodland 1983). A further specimen from the cervix was wiped on a teflon slide. The material was fixed with acetone and transported to the laboratory within 4 h. The slide was stained with a fluorescein-labelled monoclonal antibody (Chlamyset, Orion Diagnostica, Espoo, Finland) and examined for chlamydial elementary bodies using a fluorescence microscope. Chlamydial infection was diagnosed if ≥10 elementary bodies could be detected. In 122 patients, serological testing for chlamydiae was performed using an immunofluorescence test. Blind antimicrobial therapy could be instituted at this stage if felt appropriate, the standard regimen being doxycycline and metronidazole if pregnancy had been excluded.

Results of gonococcal cultures were always available within 24 h, and it was intended that the result of the Chlamyset would also be available within that time, although sometimes pressure of work on the laboratory resulted in delays. Results of chlamydial culture took approximately 7 days. Where positive results were found before the woman left the hospital, she was interviewed again by G.R.S. or C.T., the diagnosis was explained and the importance of examining sexual contacts was emphasized. Appropriate antimicrobial therapy was instituted and further follow-up with tests of cure and contact tracing was continued in the outpatient clinic of the genitourinary medicine department at the Royal Infirmary of Edinburgh. If the patient had been discharged from hospital before the discovery of positive results, she was contacted by telephone (if feasible, or letter if not) by the gynaecology firm, who informed the patient of the diagnosis and gave an appointment for follow-up and contact tracing at the genitourinary medicine department.

Results

A total of 165 patients with a mean age of 23·9 years (range 16–42 years) was screened. *C. tra-*

Table 1. Age groups of patients

Age groups	No. of patients	No. in whom STD was detected
15–19	43	11
20–24	54	14
25–29	42	5
30–34	13	0
35–39	10	2
>40	3	0
Total	165	32

chomatis alone was detected in 21, *N. gonorrhoeae* alone was detected in five and dual infection was present in six patients, giving a total of 32 (19%) patients in whom a sexually transmitted disease (STD) was detected. The age groups of the patients plus numbers in whom STD was detected are presented in Table 1. It can be seen that the bulk of positive results was found in women aged 16–29. There were, however, two women aged 37 in whom chlamydial infection was diagnosed.

The clinical diagnosis was made in 158 patients; the case notes of the other seven could not be traced, and therefore they could not be placed in any diagnostic category. A precise diagnosis was only possible in 50 (32%) patients who underwent diagnostic laparoscopy. In these patients PID was diagnosed with certainty in 12 and was thought probable in three, based on standard diagnostic criteria (Jacobson & Westrom 1969). Of the other 35, ectopic pregnancy was diagnosed in eight, ovarian cyst in seven, endometriosis in three and no pathology was found in 17 patients. Of the remaining 108 patients, PID was strongly suspected in 30, probably present in 28, and very doubtful in 50. Again these observations were based on standard diagnostic criteria (Hare 1986), and categorization was made without knowledge of the results of bacteriological investigation. A comparison of probable clinical diagnosis versus detection of STD is presented in Table 2. It can be seen that of the 42 patients with PID strongly suspected on laparoscopic or clinical grounds, STD was diagnosed in 17 (40%). Alternatively, if one considers that all the patients had PID apart from those with normal laparoscopic findings, then 30/123 (24%) had an STD. The true rate of STD in PID in this group will clearly lie within these two percentages. It is of interest that chlamydial infection in two patients was thought not to be related to the patient's symptoms.

Comparison of diagnostic methods

In all 11 women with gonococcal infection, *N. gonorrhoeae* was isolated following direct plating on to MYNC medium. One cervical specimen placed in Amies transport medium was unfortunately discarded before culture could be attempted, but *N. gonorrhoeae* was isolated from the other 10 specimens. Gonococcal isolation was achieved from only six of 11 dry high vaginal swabs.

The results for chlamydial detection were more complex. In two specimens, chlamydial culture alone was positive. One of these two had insufficient cellular material on the immunofluorescence slide for diagnostic purposes, the second test was definitely negative. In 10 cases both cultures and the immunofluorescence tests were positive. In 15, the immunofluorescence test alone was positive.

Follow-up and contact tracing

Of the 32 patients with STD, 24 were followed up in the genitourinary medicine department. Repeat tests for *N. gonorrhoeae* and *C. trachomatis* were negative in all of them. Sixteen sexual partners were also traced and examined subsequently in the department. Of the five women with gonococcal infection alone, one contact was seen and culture from the urethra was negative on two occasions. He denied the

Table 2. Clinical diagnosis of PID and laboratory detection of STD in 158 patients

	Laparoscopic diagnosis			Clinical diagnosis		
	PID+	PID±	PID−	PID+	PID±	PID−
No. of patients	12	3	35	30	28	50
No. of patients with STD	2	1	0	15	10	2

STD, Sexually transmitted disease, PID, pelvic inflammatory disease; +, classical; ±, probable; −, improbable recent use of antibiotics. Of the six women with dual infection, three contacts were examined. *N. gonorrhoeae* was isolated in all three. Chlamydial culture was negative in one, and unfortunately was not performed in the other two. Of the 21 women with chlamydial infection alone, 12 contacts were examined. Although chlamydia was not cultured from the urethra in any of the 12, nine patients were found to have non-gonococcal urethritis (NGU), defined as >10 pus cells per high-power field (×100) in a Gram-stained smear of urethral exudate. In addition, one contact with NGU had bilateral conjunctivitis, with *C. trachomatis* being cultured from both eyes. Of 13 women in whom chlamydia was detected by immunofluorescence alone, seven contacts were examined, of whom five had NGU.

None of the sexual contacts had symptoms suggestive of genitourinary infection. The only male with any symptoms at all was the individual with conjunctivitis, for which he had been attending the Eye Pavilion where topical treatment had been prescribed with no response. His conjunctivitis resolved following a course of doxycycline, and repeat chlamydial cultures from both eyes were negative.

Discussion

This was not a study of the prevalence of infection with *N. gonorrhoeae* and *C. trachomatis* in women with PID. The degree of patient selection and lack of routine laparoscopy to confirm the diagnosis preclude that possibility. Rather we have attempted to show that young women admitted to gynaecology units with lower abdominal pain represent a high-risk group for STD, and we believe that similar results would be obtained in any gynaecology unit in the UK. We would encourage that such patients should be routinely screened for STD in the same way that patients are routinely screened for ectopic pregnancy and ovarian cysts. It seems unrealistic to expect that standard genitourinary methods for diagnosis would be employed, and in their place we would suggest the combination of an endocervical swab placed in Amies transport medium for gonococcal isolation and an endocervical slide for immunofluorescence detection of chlamydiae.

For gonococcal isolation, direct plating on to MNYC in this setting has proved impractical in our experience, due to difficulties with the appropriate handling of culture plates before their use, and to the relative difficulty in obtaining access to an incubator with a CO_2-enriched atmosphere. In screening for gonococcal infection, it is advocated that material should also be obtained from the urethra and rectum in addition to the cervix (Young *et al.* 1979). However, we feel that in the setting of PID where infection ascends from the cervix, a specimen from this site alone is adequate for diagnostic purposes.

It is interesting that immunofluorescence testing and chlamydial culture gave such disparate

Table 3. Data relating to 15 patients with chlamydial infection detected by immunofluorescence alone

Index patient	Chlamydia culture	Chlamydial serology	Additional information
1	Toxic	NK	Repeat chlamydial culture positive
2	Negative	1:512	Contact diagnosed as having NGU
3	Negative	1:256	Laparoscopic diagnosis of PID
4	Negative	1:16	Laparoscopic diagnosis of PID
5	Negative	NK	Concomitant gonococcal infection
6	Negative	1:256	Laparoscopic diagnosis of PID
7	Toxic	1:256	Nil
8	Negative	1:32	Repeat immunofluorescence test negative
9	Toxic	1:8	Contact diagnosed as having NGU
10	Negative	Negative	Concomitant gonococcal infection
11	Negative	1:128	Nil
12	Negative	Positive*	Contact had chlamydial conjunctivitis
13	Negative	NK	Course of co-trimoxazole 3 weeks previously
14	Negative	Negative	Nil
15	NK	NK	NK

NK, Not known; NGU, non-gonococcal urethritis; PID, pelvic inflammatory disease.

* No titre available

results. We believe that the positive immunofluorescence results were genuine, and Table 3 shows corroborative evidence (if any) in these cases which supports this belief. A recent study has also produced evidence that immunological methods for detecting chlamydiae may be more sensitive than cell culture in women with PID (Mahony *et al.* 1987).

For the detection of chlamydial infection, immunofluorescence offers many advantages over culture. First it is quicker, with results theorectically available within 30–60 min. Handling of the specimen is simpler and does not require access to a −70°C freezer, as is the case for specimens taken for chlamydial culture (Evans & Woodland 1983). Although it is impossible to define precisely the accuracy of the test, most workers are satisfied with the specificity and the sensitivity (Thomas *et al.* 1984).

As with any STD, contact tracing is mandatory, and in keeping with previous studies (Jacob *et al.* 1987), we found a significant number of infected male partners. The fact that all the sexual partners with gonococcal or non-gonococcal urethritis were symptomless makes it unlikely that they would have sought medical attention, thus allowing them to act as a potential source of reinfection.

Women with lower abdominal pain will continue to be managed in gynaecology units, and this should continue to be the case in view of the frequency with which operative intervention is required. However, in view of the high frequency of STD in such a population it is essential that gynaecologists familiarize themselves with and implement the basic principles of management of STD with particular regard to diagnosis, treatment and contact tracing. Optimal patient care requires joint management, and a burden therefore falls upon genitourinary physicians to be available for consultation.

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Discrepancy between curettage and hysterectomy histology in patients with stage 1 uterine malignancy

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Summary. Histology reports of endometrial curettage and hysterectomy specimens were compared in patients with stage 1 uterine malignancy. In 63 of 117 (54%) the tumour grade or type reported in the curettage specimen differed from that described in the hysterectomy specimen; the grading was as likely to be more as less well differentiated at hysterectomy. The differences were not related to endometrial sampling technique or pre-operative intracavity radiotherapy. The results suggest that if decisions about patient management continue to be based on histological grading of tumours in endometrial curettage samples, unnecessary morbidity will be caused to some patients and inadequate treatment will be given to others.

Histological examination of endometrium, obtained by curettage under general anaesthesia or outpatient aspiration, is the diagnostic test used to investigate a clinical suspicion of endometrial malignancy. Stage 1 endometrial carcinoma is commonly treated by total abdominal hysterectomy, bilateral salpingo-oophorectomy and removal of the upper vagina. Some authors recommend more radical surgery with a higher morbidity, such as para-aortic lymphadenectomy or Wertheim's hysterectomy, if the tumour is found to be poorly differentiated on histological examination of the curettings (Lewis *et al.* 1970; Monaghan 1988). Similarly, when the curettings are reported as moderate or poorly differentiated, some advocate pre-operative external beam radiation, which is associated with morbidity (Salazar *et al.* 1978; Joslin 1988). Previous studies have demonstrated the fallibility of curettage in detecting endometrial malignancy (MacKenzie & Bibby 1978; MacKenzie 1985); this report compares histology of the curettage sample with that of the subsequent hysterectomy specimen.

Patients and methods

Details of 131 patients with stage 1 endometrial malignancy managed in our departments by both endometrial curettage and hysterectomy between 1 January 1980 and 31 December 1986 were studied retrospectively. The histology report of the curettage sample did not specify the tumour grade in 14 and these were excluded. The specimens were examined as part of the routine pathology service and so the curettings and hysterectomy were usually examined by different pathologists.

Endometrial samples were taken by cervical dilatation and curettage under general anaesthesia in 99 women and by outpatient aspiration curettage in the other 18 (MacKenzie 1985; Monaghan 1986). In 38 patients, pre-operative radiotherapy, consisting of a single insertion of caesium using a line source aiming to provide

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2600 cGy at Manchester point A, was given approximately 72 h before surgery. The decision to give pre-operative intracavity radiotherapy was made at the discretion of the consultant gynaecologist in consultation with the radiotherapist but was not influenced by the histology of the curettings. Progestogens were not given to any patient before hysterectomy.

The endometrial and hysterectomy specimens were classified by histological type (atypical hyperplasia, adenocarcinoma or other) and by grade of histology (well, moderate or poor differentiation) based on morphological criteria following established techniques (Rosai 1981). The number of days between endometrial curettage and hysterectomy was recorded. The hysterectomy histology included five adenosquamous lesions, two carcinosarcomas with heterologous elements, one clear-cell tumour and one uterine sarcoma.

The χ^2-test with Yates' correction was used to assess contingency tables, and Student's t-test was used to compare means.

Results

A difference between the histology reports of curettage and hysterectomy specimens occurred in 63 of the 117 cases (54%) (Table 1). The frequency of histological discrepancy was not significantly different when the endometrial sample was collected by outpatient aspiration (8 of 18 cases (44%)) or curettage under general anaesthesia (55 of 99 cases (55%)) (χ^2 = 0·38, $P = 0{\cdot}54$).

There was no significant effect of pre-operative radiotherapy on the frequency of discrepancy between the histology reports of endometrial curettage and hysterectomy specimens; a difference was found in 40 of the 79 (51%) patients treated by surgery alone and in 23 of the 38 (61%) who received pre-operative radiotherapy ($\chi^2 = 0{\cdot}65$, $P = 0{\cdot}42$). However, all six patients in whom no tumour was found at hysterectomy had received pre-operative radiotherapy.

Three of the 63 (5%) cases of histological discrepancy were of tumour type. A diagnosis of adenocarcinoma made in two endometrial samples was changed to uterine sarcoma and carcinosarcoma with heterologous elements respectively after hysterectomy. In one case a diagnosis of adenosquamous carcinoma in the endometrial sample was revised to adenocarcinoma after hysterectomy.

The hysterectomy histology was as often more as less favourable than that described in the endometrial specimen in the 54 cases in which differences of adenocarcinoma grading occurred (excluding the six in which no tumour was found at hysterectomy and the three in which there was a difference of tumour type) (Table 2). The mean (SD) time interval between endometrial sampling and hysterectomy was slightly longer (mean 29·7, SD 23·8 days) in those patients where there was a discrepancy in the histological findings than those in which the reports agreed (mean 22·4, SD 15·6 days; $P = 0{\cdot}054$). However, this trend was largely produced by the eight patients in whom endometrial atypical hyperplasia was diagnosed at curettage but adenocarcinoma was found at hysterectomy (mean interval between the procedures was 48 days, range 1–93 days).

Discussion

There was a difference between the histology report of the endometrial and hysterectomy

Table 1. A comparison of the histology reports of endometrial curettage samples with the hysterectomy specimens from 117 patients

Hysterectomy histology	Endometrial histology					
	Hyperplasia	Well	Moderate	Poor	Other	Total
No tumour	—	2	4	—	—	6
Hyperplasia	—	—	1	1	—	2
Well	7	15	20	2	—	44
Moderate	1	10	25	4	1†	41
Poor	—	2	6	12	—	20
Other	—	—	1†	1†	2*	4
Total	8	29	57	20	3	117

* One of these was a clear-cell tumour and the other a carcinosarcoma with heterologous elements.

† Described in the text.

Table 2. Effect of the hysterectomy histology on prognosis in 54 patients with adenocarcinoma by difference in grading reported from the curettage histology

	Difference in tumour grade between hysterectomy and curettage histology			
Effect on prognosis	1	2	3	Total
Improved	24	3	1	28
Worsened	23	3	—	26

specimens in 54% of the cases studied. In most cases these differences were by one grade of tumour differentiation, but in 6% the differences were by two or more tumour grades including one in which poorly differentiated adenocarcinoma was described in the endometrial sample and only hyperplasia was found at hysterectomy. In 8% the classification of tumour type was changed after hysterectomy; so overall there were major histological discrepancies in 14% of the cases studied. Possible explanations considered for the differences included: inadequate sampling by curettage, effects of pre-operative radiotherapy, changes in the tumour with time, fragmentation of the specimen at biopsy, and intra- and inter-observer variation in histological assessment. These are discussed in turn.

The technique used to sample endometrium was not the cause of the difference between the histology of curettage and hysterectomy specimens, because differences occurred whether the endometrial specimens were obtained by outpatient aspiration curettage or formal cervical dilatation and curettage under general anaesthesia. Similarly, a discrepancy occurred as often in the women treated by surgery alone as in those receiving pre-operative caesium, although in six no endometrial tumour was found at hysterectomy after pre-operative radiotherapy had been given. This is likely to have been the result of the radiotherapy rather than spontaneous regression, complete removal by curettage or a false-positive endometrial diagnosis, because it did not occur in the patients who did not receive pre-operative radiotherapy.

A change of tumour grade with time did not appear to be the explanation for the difference in histology. The time between endometrial sampling and hysterectomy was similar in the patients where the histology reports agreed to those where they disagreed. Furthermore, an improved or worsened prognosis was equally likely after hysterectomy and it is difficult to contemplate a change to greater differentiation with progression of malignant disease. There was a longer time between the procedures in the eight women in whom the endometrial samples were reported as hyperplasia but adenocarcinoma was found at hysterectomy, but this probably reflected less urgency in the management rather than the delay allowing progression to malignancy by the time of hysterectomy.

More tissue is available for study after hysterectomy than curettage and the tumour can be examined in an unfragmented form. The grade can vary in different parts of a tumour and a curettage specimen may not be representative. Histological grading of tumours in hysterectomy specimens helps predict the patients' prognosis (Keller *et al.* 1974; Jones 1975) and so this assessment of endometrial tumours is useful. It seems likely that when differences occur, the histology of the hysterectomy would be more reliable than the curettage specimen.

Histological grading of a malignant tumour is subjective and so when a tumour is examined in two specimens, often by different pathologists, variation in the reports will occur. It is possible that the differences detected in this study merely reflect variation in interpretation of tumour grading. This could be resolved by a review of both the curettage and hysterectomy specimens by a single pathologist. However, whatever the causes of the discrepancies, it is the information available to the clinician when decisions about management are made that is important and this was examined in the present study.

The implications of these findings are considerable if presurgical or surgical management is based on curettage results. Some workers advocate that when poorly differentiated tumour is found at curettage the patient should receive either pre-operative radiotherapy (Salazar *et al.* 1978) or lymphadenectomy at hysterectomy (Monaghan 1988). Our findings suggest that these policies would result in up to half the patients having unnecessary added morbidity, while others would be undertreated.

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An explanation for the problem of false-negative cervical smears

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Summary. False-negative cervical cytology due to sampling error is a well-recognized problem. Forty-seven women with histologically proven cervical intraepithelial neoplasia (CIN) were studied. All had two cervical smears performed at a mean interval of 3 months. At the time of the second smear, cervicography, colposcopy and biopsy were performed. The area of acetowhite cervical lesions and of the total visible atypical transformation zone (ATZ) were measured from the cervical photographs. The 17 women in whom one or both smears showed no dyskaryosis were found to have a significantly smaller proportion of their ATZ affected by CIN. It is suggested that this finding can account for the sampling error which causes false-negative cervical cytology. New screening techniques, such as cervicography, may offer a method of detecting and assessing these relatively smaller cervical lesions.

The problem of false-negative cytology is well recognized, but estimates of its frequency have varied greatly: from 6 to 55% for invasive carcinoma (Richart & Vaillant 1965; Berkowitz *et al.* 1979), 19 to 45% for carcinoma *in situ* (Creasman & Rutledge 1972; Sedlis *et al.* 1974) and 28 to 50% for dysplasia only (Richart & Vaillant 1965; Coppleson & Brown 1974). The report of the Intercollegiate Working Party on Cervical Cytology Screening (1987) commented 'false negatives can occur and the percentage increases when laboratories are working under excessive pressure', thereby implying that screener error may be a significant cause of this problem. However, previous studies (Fetherston 1983) have suggested that sampling error is the major cause of false-negative cytology, with various remedies such as paired sampling (Beilby *et al.* 1982) or a specifically designed spatula (Hussain 1986) being proposed.

A recent study (Hartman *et al.* 1986) examined cone biopsy specimens from women who had false-negative cytology confirmed by repeat smear assessment, and concluded that the errors were due to small endocervical lesions being missed by conventional cytological sampling. However, the value of this study is limited by the authors' selection criteria for cone biopsy comprising positive endocervical cytology or endocervical extension of a colposcopically visible lesion. Thus the interpretation of their findings is restricted to this particular group of women only.

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Table 1. A comparison of the measured areas for those cases with and without episodes of false-negative cytology

	False-negative smear ($n = 17$)	Correct smears ($n = 30$)	P value*
Median acetowhite area (AW) (mm²)	19·2	21·9	0·15
Median area ATZ (mm²)	46·4	44·6	0·34
Median ratio AW/ATZ (%)	26·0	53.8	0·0004

* Using the Wilcoxon rank sum test with two-sided significance levels.

It has been suggested (Stafl 1981) that the additional use of a photographic record of the cervix may reduce the frequency of false-negative diagnoses of cervical neoplasia. This technique, called cervicography, provides an accurate record of the colposcopic appearance of the cervix. Although it has been used (Darnell Jones *et al.* 1987) to assess women presenting with abnormal cervical smears, its value in large population screening programmes remains to be proven.

In this study, we have used cervicography recordings to measure the total area of the atypical transformation zone (ATZ) and of any abnormal cervical epithelium within it. These measurements were then related to the occurrence of false-negative cytology in cases of histologically proven cervical intraepithelial neoplasia (CIN).

Subjects and methods

In March 1987 a colposcopy clinic was established in a family planning clinic in Islington, London. All women attending the clinic were offered a referral for colposcopic screening to supplement their regular cervical smear. In addition, all women found to have abnormal cervical cytology were referred for colposcopic investigation.

Each woman had a standard history taken and then a repeat cervical cytology smear was obtained before colposcopy was performed. The cervical appearance was recorded using a fixed-focus camera specially designed for cervicography (National Testing Laboratories, St Louis, Missouri, USA). One photograph was taken after the application of 5% acetic acid, and another after the application of aqueous iodine solution Colposcopically directed biopsies of abnormal epithelium were then taken for histological analysis. Standard criteria were used for both the histological (Buckley *et al.* 1982) and cytological (Evans *et al.* 1986) assessment of specimens in this study.

The cervicograph photographs were analysed quantitatively with a MOP-Videoplan image analyser (Kontron Electronic Group). The slides were projected on to the digitizing tablet from a fixed distance (1·33 m), and the required areas traced with the pen to obtain a measurement of area in square millimetres. Firstly, the picture taken after the application of 5% acetic acid was used to measure the area of surface epithelial abnormality. Then the area of the visible ATZ was measured using its lack of iodine uptake by the non-glycogenated epithelium as a marker. The ratio of the area of acetowhite epithelium to the total ATZ area was expressed as a percentage. All measurements were performed at one sitting, with no movement of the projector or the digitizing tablet between measurements. The results were analysed using the Wilcoxon rank sum test and two-sided significance levels.

Results

Of 50 consecutive women found to have histological evidence of CIN, 47 had a set of

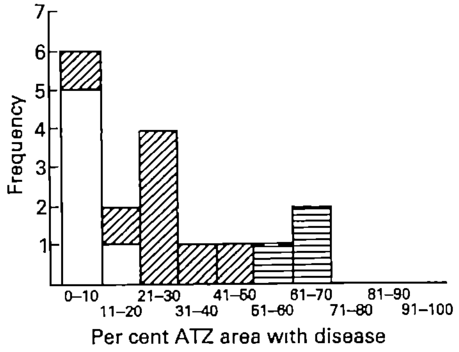

Fig. 1. The distribution of grade of CIN by the percentage area of the atypical transformation zone with disease, for cases of false-negative cytology. □, CIN I, ▨, CIN II; ⊟, CIN III.

cervicography photographs which were technically suitable for study. The mean interval between the smear performed in the family planning clinic and the one obtained at the time of colposcopy was 3 months (range 1–4 months). A total of 30 women had dyskaryosis on both slides, but 17 women had at least one smear reported as normal, even after review by a senior cytologist. Four of these women had no dyskaryosis on either smear, having been referred with normal smears for colposcopic screening. Thirteen had initial smears showing mild dyskaryosis and subsequently normal smears.

The median measurements of acetowhite area, atypical transformation zone (ATZ) area and their ratio, expressed as a percentage, are shown for each group in Table 1.

There was no significant difference in the measured area of the ATZ between the two groups ($P = 0{\cdot}34$). The size of the lesions was slightly smaller in the group with false-negative cytology, but this was not statistically significant ($P = 0{\cdot}15$). However, there was a significant correlation ($P = 0{\cdot}0004$) between false-negative cytology and the ratio of acetowhite area to the total ATZ area expressed as a percentage.

The histological grades of the lesion for each group and their distribution by the proportion of the ATZ showing disease are shown in Figs 1 and 2.

There were no significant differences in the ages, marital status, parity or contraceptive use of the women between the two groups. The mean time elapsed between the two cervical smears was similar in the two groups.

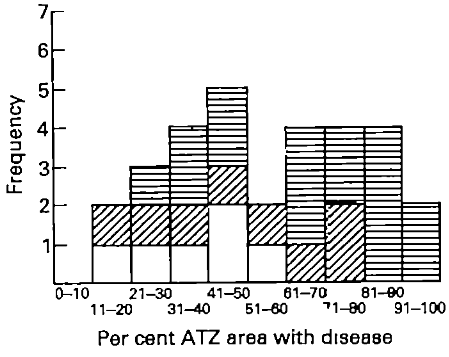

Fig. 2. The distribution of grade of CIN by the percentage area of the atypical transformation zone with disease, for cases of correct cytology. □, CIN I; ▨, CIN II; ▤, CIN III.

Discussion

This study demonstrates that false-negative cytology due to sampling error is commoner in women who have a smaller proportion of the visible cervical ATZ affected by CIN. This can be interpreted as indicating that sampling for CIN lesions which constitute a small fraction of the ATZ is relatively difficult. That may be due to either the small area occupied by the lesion or the large extent of the transformation zone and may further explain the suggestion (Rubio 1977) that small lesions escape cytological detection by eluding the trapping phenomenon in cell sampling. Our data suggest that the concentration of abnormal cells required to reach the threshold for detection may be directly related to the fraction of the ATZ affected by CIN.

One-third of the cases of false-negative cytology occurred with lesions occupying less than 10% of the area of the ATZ; the histology of these lesions was almost entirely CIN I. Indeed, 14 of the 17 cases of false-negative cytology had only CIN I or II lesions present, all occupying less than 50% of the ATZ. This suggests that most women with false-negative cytology have smaller lesions of low histological grade. The association of smaller lesions with lesser grades of CIN has been suggested previously (Abdul-Karim *et al.* 1982) and, if true, may partly reassure us that those women at highest risk from false-negative cytology may be the women with the least severe histological grade of disease.

The report of the Intercollegiate Working Party on Cervical Cytology Screening (1987) recommended that women with mild dyskaryosis should be managed with repeat smears at, say, 3–6 months. Using this method of follow-up, three cases of CIN III would have been missed by false-negative cytology, which suggests that the management of women with mild dyskaryosis should take the form of colposcopy and directed cervical biopsy for histology. On the other hand, the finding that cervicography detected all the cases of CIN in this study suggests that its use as a screening method alone, or in conjunction with cytology, merits further assessment.

Acknowledgments

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Invasive cancer of the cervix after laser treatment

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Summary. Over a period of 8 years and 6 months, 1979–1988, 4222 women were treated with laser ablation for cervical intraepithelial neoplasia (CIN) with or without papillomavirus infection of the cervix. Of 3738 patients followed up, nine were diagnosed as having invasive cancers of the cervix, four of which were microinvasive. It is stressed that each woman treated with laser must have frequent, long-term cytological follow-up.

Laser ablation is an accepted technique for the treatment of cervical intraepithelial neoplasia (CIN) and human papillomavirus infection (HPV) of the cervix. An indication of the success of this technique may be gained from the study of rates of recurrent cervical abnormalities and in particular the rate of development of invasive cervical carcinoma after treatment There are currently no figures available concerning such risks, although a previous report from this department mentions one case (Ali *et al.* 1986).

Jordan (1985) defines strict criteria of suitability for laser ablation. (i) The entire lesion must be visible on the ectocervix; (ii) there must be no suggestion of invasive cancer on cytology, colposcopy or histology; and (iii) the histological report must be available before treatment.

Patients and methods

In the Regional Department of Gynaecological Oncology 4222 patients meeting the above criteria were treated with laser ablation during the period September 1979 to February 1988. The techniques of colposcopy and laser treatment were as described previously (Evans & Monaghan 1983; Evans *et al.* 1984; Ali *et al.* 1986). The laser used was a Coherent System 400. Most patients were treated as outpatients without analgesia or anaesthesia. Some had local anaesthetic injected into the cervix and a small percentage had general anaesthesia because of extensive lesions, pain or extreme apprehension.

The follow-up schedule initially consisted of colposcopic and cytological review at 3-month intervals with a gradual lengthening of this interval and increasing reliance on cytology alone. Currently, patients are reviewed once cytologically and colposcopically at 6 months after treatment and thereafter are followed using the departmental computer, smears being taken by their general practitioners.

All the patients' records are computerized and regularly updated by the medical staff.

Patients who develop further cytological abnormalities are reviewed colposcopically and any histologically proven recurrence is treated by repeat laser or cone biopsy or, more rarely, hysterectomy.

Results

The initial histology reports leading to the treatment of the 4222 patients are summarized in Table 1.

Of these 4222 patients 484 have not yet had their first cytological follow-up and are therefore excluded from the following analysis. The remaining 3738 have been followed up for at least 6 months each. Table 2 indicates the length of follow-up of patients within the study period using a life-table method of analysis.

Although 3392 of 3738 patients (91%) had

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Table 1. Distribution of patients by initial histology report

Initial report	No. of patients
CIN I	168
CIN II	508
CIN III	2193
CIN plus HPV	734
HPV only	602
Not recorded	17

HPV, Human papillomavirus, CIN, cervical intra-epithelial neoplasia.

clearance of their lesions with one treatment, 346 required further measures. Of these a total of 267 patients had repeat laser performed on at least one occasion for recurrent histologically demonstrated CIN or human papillomavirus infected tissue. Twelve of these were treated twice more and one patient had three retreatments.

Cone biopsy was performed in 62 patients for recurrent abnormalities.

Sixteen patients underwent hysterectomy for recurrent or persistent disease. Nine of these were for persistent CIN III and four were for microinvasion found at cone biopsy. The remaining three patients had other gynaecological problems as well as minor cytological and histological abnormalities.

A further 30 patients had non-malignant gynaecological problems warranting hysterectomy with no cytological abnormality.

In addition to the four patients mentioned above who developed microinvasive cancer a further five patients have developed invasive cancer of the cervix following laser ablation. These are described in detail below.

Patient no. 1

The first patient had been reported previously (Ali *et al.* 1986). She was treated in 1983 after a colposcopic biopsy which showed CIN III with gland infilling; however, at diagnosis some 6 months later she had a Stage IIIb squamous carcinoma of the cervix. After an initially good response to radical radiotherapy she developed a recurrence in 1986 and died of the disease in December 1987.

Patient no. 2

This patient had laser ablation for CIN III in 1983 with subsequent normal smears in 1983, 1984 and 1985. A smear taken in September 1986 showed severe dyskaryosis, and an invasive large-cell squamous carcinoma Stage Ib was diagnosed. She is currently alive without disease following radical hysterectomy.

Patient no. 3

The third patient had laser ablation in 1985 for CIN III. Subsequently she had a negative smear in 1986, followed by a smear showing borderline changes in March 1987. She returned to the colposcopy clinic in November 1987 and was diagnosed as having a Stage Ib squamous carcinoma of the cervix. Assessment of the para-aortic nodes showed these to be the site of metastatic disease. She has been treated with pre-operative chemotherapy, radical hysterectomy and post-operative radiotherapy.

Patient no. 4

The fourth patient had laser ablation in 1984 for CIN III with gland infilling. She had negative smears in 1984, 1985 and 1986. In 1987 a smear showed severe dyskaryosis, and colposcopically directed biopsy and subsequent cone biopsy showed a very early invasive adenocarcinoma of the cervix. She has had a total hysterectomy but there was no residual disease.

Patient no. 5

The fifth patient had laser treatment for cervical warts in 1982. She was a poor attender for follow-up but in December 1987 she was found to have a cervical squamous carcinoma. She is

Table 2. Life-table analysis of length of follow-up

Year after treatment	No. of patients at start of year	Exposed to risk of cancer throughout the year
0	3738	3186
1	2633	2155
2	1676	1353
3	1026	807
4	588	452
5	316	232
6	148	99
7	50	31·5
8	13	7
9	1	1

Table 3. Life-table analysis of occurrence of cervical cancer

Year after treatment	No of cancers developed during the year	Proportion without invasive disease from treatment to end of each year
0	1	1·000
1	2	0·999
2	4	0·996
3	1	0·995
4	0	0·995
5	1	0·990
6	0	0·990
7	0	0·990
8	0	0·990
9	0	0·990

currently alive without disease after radical hysterectomy.

In summary, cervical carcinoma occurred in nine of the 3738 patients over the study period (five invasive carcinomas and four microinvasive). A life-table type analysis of this is shown in Table 3. The 5-year rate of development of invasive disease was 0·5% The longest time from laser treatment to development of the disease was between 5 and 6 years, giving a 6-year risk of invasive disease of 1·0%.

Discussion

In this survey laser ablation was effective in clearing the cervical lesions in 3392 of 3738 patients. However, the development of nine cases of invasive carcinoma emphasizes several important points in the employment of this method of treatment.

(i) In view of the subsequent history it is likely that patient no. 1 had invasive disease at the time of laser treatment. The need for a uniform, high standard of colposcopic assessment by experienced staff is stressed with no laser treatment being given if there is any suspicion of invasion.

(ii) The colposcopically directed biopsy is vitally important in determining the mode of treatment. An adequate number of biopsies must therefore be taken to prevent the possible false-negative results of sampling an area of minimal abnormality. The biopsy must also include cervical stroma if invasion or microinvasion is to be excluded.

(iii) After laser ablation malignancy may develop either from residual areas of CIN or papillomavirus infection or from *de novo* development. Adequate depth of initial treatment (Anderson & Hartley 1980) and an adequate margin surrounding the area of visible abnormality are therefore important in reducing the risk of residual affected areas.

(iv) In this series the longest time from treatment to development of invasive disease was between 5 and 6 years. The need for long-term follow-up is therefore emphasized. As colposcopy services have enlarged, the problem of following huge numbers of patients has necessitated efficient organization of the intensity of follow-up. In this department initial colposcopic and cytological follow-up is rapidly succeeded by cytological follow-up alone relying on computerization of records and an accurate recall system. In this series very few patients have been lost to follow-up and it appears that cytology alone is adequate to allow early recall of patients with persistent or recurrent abnormalities as well as those with early invasive cancer. The interval for screening has so far been annual.

We recommend that long-term annual cytological review should be the minimum requirement for patients treated with laser ablation.

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Subclinical intra-amniotic infection with *Gardnerella vaginalis* associated with preterm delivery. Case report

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Case report

In 1984 a 34-year-old primigravida was admitted at 33 weeks gestation with a history of premature rupture of membranes. Ten days later she gave birth to a fresh stillborn female child weighing 2 kg. Blood cultures grew an enterococcus, and autopsy confirmed a fetal infection. In April 1986 she gave birth to a healthy 3·1-kg girl.

In her third pregnancy she was admitted to St Mary's Hospital at 30 weeks gestation with irregular contractions. She was apyrexial, and examination confirmed a normal 30 week pregnancy with no uterine tenderness. The cervix was posterior, soft and closed. No amniotic fluid was seen to be draining and this was confirmed by a negative nitrazine test. Over the next 6 h labour became established and intravenous salbutamol was started. After a further 3 h the white cell count was found to be $24\cdot5 \times 10^9$/l. Microscopy of the urine and high vaginal swab were negative. The level of C-reactive protein, a sensitive acute phase protein which rises in the initial stages of inflammation, was 96 mg/l, suggestive of active infection (Fisk *et al.* 1987). The patient was still apyrexial and asymptomatic. An ultrasound scan estimated fetal weight to be 1350 g. Fetal breathing was not seen. A 20 ml volume of clear amniotic fluid was aspirated by amniocentesis. Microscopy revealed many neutrophils and multiple, pleomorphic Gram-negative rods. A subclinical intrauterine infection was diagnosed and in view of the previous stillbirth she was delivered by a lower-segment section of a live female child weighing 1·32 kg. The baby made good progress in the special care baby unit and was discharged after 4 weeks. Her mother also had an uneventful postoperative recovery.

Microbiology results

The high vaginal swab taken before delivery grew only lactobacilli. Amniotic fluid cultures grew colonies of Gram-variable/Gram-negative rods after overnight incubation on blood agar anaerobically and in carbon dioxide. They were catalase negative and β-haemolytic on 5% human blood agar bilayer plates after 48 h in carbon dioxide (Totten *et al.* 1982). Positive α-glucosidase and negative β-glucosidase tests confirmed them to be *Gardnerella vaginalis*. The isolate was shown to be *G. vaginalis* biotype 1 by positive hippurate hydrolysis, lipase and β-galactasidase tests. This is a common biotype amongst vaginal isolates (Piot *et al.* 1984). The level of cord C-reactive protein was raised (24 mg/l).

The placenta and membranes showed no histological evidence of chorioamnionitis. However, polymorphonuclear cells are notably absent in vaginitis due to *G. vaginalis* infection (Gardner & Dukes 1955).

Discussion

Advances in neonatal care have greatly reduced perinatal mortality. Further reduction is largely dependent on a decrease in the rate of preterm delivery. There is evidence that certain maternal genital tract infections are amongst the most important preventable causes of preterm

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delivery (Gravett *et al.* 1986*a*). Group B streptococci (Regan *et al.* 1981), *Neisseria gonorrhoea* (Ampstey & Steadman 1976), *Chlamydia trachomatis* (Martin *et al.* 1982), *Ureaplasma urealyticum* (Kundsin *et al.* 1984) and herpes simplex virus (Nahmias *et al.* 1971) have been associated with preterm delivery. *G. vaginalis* in association with anaerobic bacteria and genital mycoplasma (bacterial vaginosis) has been found in 43% of preterm labours compared with 14% of matched controls (Gravett *et al.* 1983).

Although in our patient *G. vaginalis* was not isolated from the vaginal swab it was found in the amniotic fluid with the membranes still intact. This is the first reported case in the UK. Gravett *et al.* (1986*b*) performed amniocentesis on 54 consecutive women in preterm labour with intact membranes and isolated micro-organisms from 13 (24%) samples including *G. vaginalis* in three of them. *G. vaginalis* is thought to produce high amounts of phospholipase A2 This hydrolyses the ester bonds of the phospholipids in the amnion and chorion releasing arachidonic acid, a precursor for prostaglandin synthesis (Begar *et al.* 1981). Prostaglandin production may then trigger the onset of preterm labour.

In our patient the early diagnosis of a subclinical infection was based on a raised white cell count, C-reactive protein levels and amniocentesis. There is growing evidence to support the use of C-reactive protein as an early diagnostic marker for chorioamnionitis (Fisk *et al.* 1987). It precedes maternal fever by 17–34 h and uterine activity by 17–28 h (Romem & Artal 1984). The method is non-invasive, repeatable and can be used in all patients (Hawrylyshyn *et al.* 1983). Amniocentesis is invasive and not always possible if there is little amniotic fluid (Garite & Freeman 1982). We suggest that a raised C-reactive protein level in the absence of obvious infection indicates the need for amniocentesis and possible active management.

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Favourable neonatal outcome following maternal paracetamol overdose and severe fetal distress. Case report

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Case report

A 22-year-old pregnant woman presented at 32 weeks gestation having taken 50 g of paracetamol 12 h previously, following a domestic crisis. She had also taken a 15-g paracetamol overdose the preceding week. Blood paracetamol level was 2·97 mmol/l (448 mg/l) and despite the relatively late presentation she was treated with intravenous *n*-acetylcysteine. She reported absent fetal movements, and a cardiotocograph (CTG), recorded 16 h after the overdose, showed marked decrease in variability with no accelerations (Fig. 1). Ultrasound confirmed complete lack of fetal movements and fetal breathing, but amniotic fluid volume was normal. Umbilical artery resistance index measured by Doppler ultrasound had a normal value of 0·46 (Pearce *et al.* 1988).

At 36 h after the overdose, the CTG showed marked further deterioration (Fig. 2) with a falling baseline rate in an undulating pattern with no beat-to-beat variability. Maternal prothrombin time was 1·8 times control. Aspartate transaminase (AST) was 267 i.u./l compared with 57 i.u./l on admission, but the patient did not look jaundiced. It was decided that the abnormal cardiotocographic pattern was most probably due to the paracetamol rather than to placental insufficiency, and that the fetus was unlikely to survive normal labour. Caesarean section was felt to be an unjustifiable risk for the mother in view of the magnitude of the overdose and her incipient hepatic failure. In any case, the potential benefits to the fetus of immediate delivery and exchange transfusion were unclear at that stage.

An expectant policy was followed, but the next day the AST had risen to 5269 i.u./l and the prothrombin time to 3·5 times control. Supportive therapy for imminent hepatic failure was commenced, and transfer to a transplant centre was arranged. However, it was decided to deliver the patient before she was transferred, so labour was induced with a prostaglandin pessary, the membranes were ruptured and labour augmented with oxytocin. The CTG had returned to normal by the time of labour (Fig. 3). Spontaneous vaginal delivery of a healthy female infant occurred 84 h after the overdose. Birthweight was 2198 g, Apgar scores were 9 at 1 min and 10 at 5 min, and cord umbilical artery pH was 7·29 with a base deficit of 1 mmol/l. Cord blood samples showed no measurable residual paracetamol. The mother's liver function started to improve on the day of delivery and no further maternal treatment was needed.

The infant was initially hypoglycaemic, and had a transient respiratory illness and mild jaundice. Liver enzymes were never outside the normal range (maximum AST 56 i.u./l on day 1, and 10 i.u./l by day 3) and the hyperbilirubinaemia (initial serum bilirubin 66 μmol/l on day 1, maximum value 177 μmol/l on day 4) was fully compatible with jaundice of immaturity. No biochemical or neurological abnormality was detected in the infant at follow-up aged 6 weeks and 6 months. The mother has fully recovered physically, and there have been no further overdoses.

Discussion

The conventional cardiotocographic signs of fetal distress are usually due to fetal hypoxia,

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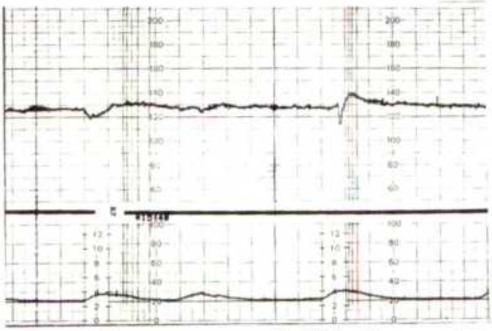

Fig. 1. Cardiotocogram recorded 16 h after overdose, showing marked reduction in heart rate variability.

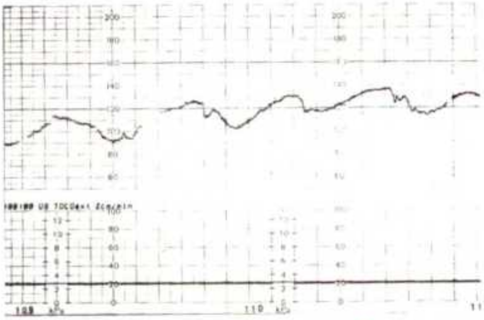

Fig. 2. Cardiotocogram recorded 36 h after overdose, showing reduced variability and baseline bradycardia.

and often indicate that delivery should be expedited. However, fetuses can be distressed by other insults, and this report shows that the CTG may be affected by the toxic effect of paracetamol. Immediate delivery may not be appropriate in such circumstances. In this patient, delivery was delayed for maternal reasons, and the fetus was born in excellent condition 3 days later. There are previous reports of successful pregnancy outcome following severe maternal paracetamol overdose (Byer *et al.* 1982; Lederman *et al.* 1983; Roberts *et al.* 1984; Stokes 1984). However, our patient was unusual in that maternal paracetamol levels were particularly high, and severe fetal distress was observed.

Lederman *et al.* (1983) described an infant of 29 weeks gestation born after a spontaneous labour, 16 h after a much smaller maternal overdose of 32·5 g paracetamol. That infant had a significant amount of paracetamol in the circulation and had exchange transfusions on four occasions with a good short-term outcome. Although the levels of paracetamol and circulating metabolites fell temporarily following exchange transfusion in that case, Roberts *et al.* (1984) reported that exchange transfusion did not affect the half-life of paracetamol in an infant of 36 weeks gestation.

Children and infants are known to be relatively resistant to the toxic effects of paracetamol, probably because they have more efficient extramicrosomal sulphation mechanisms than adults (Lieh-Lai *et al.* 1984). As a result, less of the drug is converted to potentially hepatotoxic metabolites by the microsomal mixed function oxidase pathway. It is also suggested that infants have more available glutathione to convert the reactive intermediate metabolites to the mercaptopurate conjugate (Rumack 1986). The infant described by Lederman *et al.* (1983) showed a postnatal rise in the paracetamol mercaptopurate levels. They suggest that this implied postnatal conjugation of potentially toxic metabolites with glutathione, and that neonatal glutathione stores may have been depleted if exchange transfusion had not been performed.

If an infant is born with toxic paracetamol levels, it may be prudent to perform exchange transfusion and, perhaps, to consider repleting glutathione stores by using *n*-acetylcysteine, even if there is a considerable time gap between overdose and delivery. However, in our patient we considered the possible benefit of immediate delivery to allow exchange transfusion of the newborn infant was outweighed by the risk to the fetus of labour and vaginal delivery and the risk to an ill woman of caesarean section.

The successful outcome in our patient after an extremely severe maternal overdose suggests that the conservative approach to management was appropriate. Indeed, this pregnancy might have continued uneventfully until term, had the maternal condition not precipitated preterm induction.

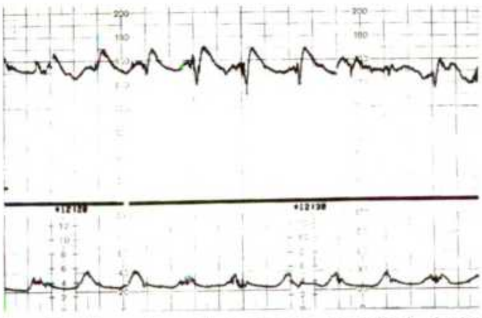

Fig. 3. Normal cardiotocogram recorded during labour.

Acknowledgments

We are grateful to Mr I. Z. Mackenzie and Dr A. R. Wilkinson for permission to report this case, and to Dr C. W. G. Redman, Dr R. W. G. Chapman, Dr H. R. Gamsu and Dr P. Mcelhatton for their advice on management. Dr Roger Williams made helpful comments on the manuscript.

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Basilar migraine with loss of consciousness in pregnancy. Case report

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Case report

The 28-year-old woman presented in her third pregnancy. She had given birth to her first child by emergency caesarean section at 33 weeks gestation because of an abruption, but her second child was born without complications. She had never had hypertension, migraines, seizures, loss of consciousness or visual disturbances.

In this pregnancy her blood pressure was 120/70 mmHg at 17 weeks gestation. She was admitted to hospital at 38 weeks when the blood pressure rose to 140/90 mmHg. She had proteinuria on admission but subsequent tests were only intermittently positive. Her blood pressure was 120–150/70–100 mmHg, but on one occasion reached 160/100 mmHg and she intermittently complained of headache. Four days after admission she was treated with amoxycillin for a presumed sinusitis. The next day she complained of severe frontal headache, dizziness, and of seeing flashing lights. Her blood pressure was 160/100 mmHg and she was noted to be drowsy. Ten minutes later she was found unconscious with a blood pressure of 130/90 mmHg. She had not vomited or been incontinent and there were no signs of trauma. Shortly afterwards, she opened her eyes when addressed, complained of headache and photophobia, but was very drowsy. She became unresponsive except to painful stimuli. There were no focal neurological signs, her neck was supple and she did not have papilloedema. The blood pressure was 130/75 mmHg and a catheter sample of urine did not contain protein. Arterial blood gases in room air, serum electrolytes and cerebrospinal fluid were normal. A toxicology screen of serum and urine was negative. Computerized axial tomography of the head showed no lesions. Electroencephalogram showed no evidence of seizure activity.

Over the next 24 h she slowly improved, and 36 h after the event she was alert and feeling well. Cultures of blood, urine, sputum and CSF were negative, and acute and convalescent viral serology did not indicate active infection.

Five days later her blood pressure rose to 160/110 mmHg, without proteinuria, but the level of aspartate aminotransferase was 106 i.u./l and uric acid was 371 μmol/l. Labour was induced and a healthy 3491 g female baby was born spontaneously. The patient's postnatal course was uncomplicated and 6 weeks after delivery she felt entirely well with a blood pressure of 120/80 mmHg, a normal aspartate aminotransferase level and a uric acid of 267 μmol/l.

Comment

This unusual event was initially thought to be eclampsia, but there was no evidence for a *grand mal* seizure and the patient remained stuporose for over 12 h. Although not persistently proteinuric, she did have new hypertension, hyperuricaemia and an elevated plasma aspartate aminotransferase activity, all of which reverted to normal after delivery and were compatible with a diagnosis of moderate pre-eclampsia.

Our final diagnosis was of vertebro-basilar migraine with underlying pre-eclampsia. Basilar migraine is a rare syndrome that has not been reported before in association with pregnancy. Its features can include bilateral disturbances of vision, ataxia, dysarthria, vertigo, tinnitus and bilateral peripheral dyaesthesiae followed by occipital headache (Bickerstaff 1961*a*). More

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relevant to our patient is that the attacks can be associated with loss of consciousness attributed to transient ischaemia of the reticular formation of the brainstem (Bickerstaff 1961*b*). Stupor lasting up to 5 days may occur (Lee & Lance 1977). The loss of consciousness is usually gradual, as it was in our patient; patients appear to be in deep sleep, but can be aroused with strong stimulation (Bickerstaff 1961*b*). The diagnosis of hysteria is often first considered. Our patient did not have a history of migraine or frequent headaches, but migraine can occur for the first time during pregnancy (Wright & Patel 1986; Callaghan 1968). In addition, an association between migraine and pre-eclampsia has been reported (Rotton *et al.* 1959; Moore & Redman 1983; Rubin & McCabe 1984) although others have refuted it (Somerville 1972; Wainscott *et al.* 1978). Duncan *et al.* (1989), using sophisticated imaging techniques, have found evidence of vasospasm in women with cortical blindness associated with eclampsia. This suggests that cerebral arterial constriction may be an abnormality common to pre-eclampsia and migraine.

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SHORT COMMUNICATIONS

Diagnostic role of dilatation and curettage in the management of abnormal premenopausal bleeding

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Dilatation and curettage is of accepted value in the diagnosis of pathology in women with postmenopausal bleeding. However, there have been few studies which have looked specifically at the role of this procedure in abnormal premenopausal bleeding. It is in this group that dilatation and curettage is perhaps overused as a diagnostic tool (Tindall 1987). With this in mind, we reviewed the histological findings from dilatation and curettage in women presenting with abnormal premenopausal bleeding.

Patients, methods and results

The notes of 356 consecutive premenopausal women who were investigated by dilatation and curettage for menstrual disturbance between January 1979 and December 1980 were obtained through theatre records and reviewed during 1986. The menstrual pattern at presentation was classified as heavy and regular or irregular, which included inter-menstrual bleeding. The histology was classified as normal if the endometrium was proliferative or secretory, all other findings being abnormal. For analysis, the patients were divided into two age groups: <40 years of age and ≥40 years of age. Throughout the study period, it had been the practice of the unit to perform dilatation and curettage as an initial procedure in women referred with menstrual disturbance.

There were 10 women with abnormal histology (Table 1), all of them were ≥40 years of age. There were two women with cystic hyperplasia who had regular heavy periods, all the other eight women had presented with irregular bleeding. The uterine leiomyosarcoma is included though this was a fortuitous finding in a woman who had fibroids with a proliferative endometrium at dilatation and curettage but subsequently she had a hysterectomy for continued irregular bleeding.

Discussion

The results show that dilatation and curettage detects a significant occurrence of pathology in women ≥40 years of age. We found that 2% had hyperplasia of the endometrium of which a third showed atypical cells, and 0·6% had endometrial carcinoma, both of which were well differentiated. Estimates of pathology in women aged ≥40 with dysfunctional bleeding vary. Ngu & Quinn (1984) found 18 out of 200 had cystic hyperplasia and three had atypia, whilst Nickelsen (1986) found hyperplasia in 3% of women with menstrual disturbance, all of whom presented with irregular bleeding and were >45 years of age. MacKenzie & Bibby (1978), in a large retrospective survey, found hyperplasia in 6·5% of 580 premenopausal women. However, none of these three studies found endometrial carcinoma in a premenopausal woman.

Conversely, no significant pathology was found in the under-40 age group in our study. The proportion of women <40 years of age with endometrial carcinoma has been variously quoted at between 0·85% and 10% (Barter *et al.* 1968; Gusberg & Mulvihill 1986) and a predicted incidence under age 36 has been calculated to be 1 per 100 000 women per year (MacKenzie & Bibby 1978). We would concur with Barter *et al.* (1968) who state that dilatation and curettage appears to be of little value in the diagnosis of endometrial malignancy in women under 40 years of age. Nickelsen (1986) found no diagnos-

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Table 1. Abnormal endometrial histology found at dilatation and curettage in 356 women

Pathology	No. of women	Age (years)
Cystic hyperplasia	5	44, 46, 46, 47, 47
Atypical hyperplasia	2	49, 53
Endometrial adenocarcinoma	2	49, 54
Uterine leiomyosarcoma	1	42

tic advantage from curettage in women below 35 years of age.

We conclude that dilatation and curettage has an important role in the diagnosis of endometrial pathology in women aged 40 or more particularly if the presentation is with irregular vaginal bleeding. In women with menstrual disorders under the age of 40, we agree with previous recommendations (Grimes 1982) that dilatation and curettage is not necessary as an initial procedure as pathology is so uncommon.

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Topical anaesthesia with lidocaine–prilocaine cream for vulval biopsy

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An increasing number of women are presenting to the clinic for sexually transmitted diseases at St Mary's Hospital with vulval diseases which range from various infections to the dermatoses and vulval intraepithelial neoplasia (VIN). In some cases, because of the special nature of vulval pathology, a biopsy is required for histological review to establish or confirm the diagnosis. Analgesia is essential in this sensitive anatomical area and hospitalization with general anaesthesia is often employed. The alternative is local infiltration anaesthesia which itself is painful and induces stress in the patient. Lidocaine–prilocaine cream (EMLA, Astra), also known as lignocaine–prilocaine cream, has been used with good effect for local anaesthesia before venepuncture (Wahlstedt *et al.* 1984) and cautery of genital warts (Hallén *et al.* 1987). We report, for the first time, its use in undertaking vulval biopsy.

Patients, methods and results

Fifteen diagnostic punch biopsies (4 mm) and one excision biopsy were performed on 10

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Table 1. Application time of lidocaine–prilocaine cream and pain experience during vulval biopsy

	Application time of cream to each site (min)		Pain score*	
Patient no.	Mucosal skin	Keratinized skin	Biopsy site 1	Biopsy site 2
1	15	20	1	3†
2	17	—	2	—
3	11	21	1	2
4	18	28	1	2
5	22	—	1	—
6	—	25	2	—
7	15 & 15	—	1	2
8	15 & 15	—	2	2
9	19	19	1	2
10	—	20	4†	—

*1 = none, 2 = slight, 3 = moderate, 4 = barely tolerable.
†Patient required additional analgesia.

patients (Table 1). About 1–2 ml of cream was applied in a thick layer to each site. A plastic film (Tegaderm) was applied over the cream, except when there was natural occlusion, as in the introitus. The site to be biopsied was tested for analgesia by probing with a needle (gauge no. 25) intermittently. Pain during the biopsy procedure was assessed on a five-point scale as follows: none, slight, moderate, barely tolerable or intolerable. The results in Table 1 show that EMLA gave sufficient analgesia to complete 14 of the 16 biopsies with no more than slight pain experienced. The application time required for analgesia of the mucosal surface (mean 16 min) was less than that required for analgesia of keratinized skin (mean 22 min). Additional infiltration with lignocaine hydrochloride (2%) was required to complete the procedure in two women. No patient complained of symptoms due to application of the cream, although local reactions of erythema and oedema of a slight to moderate degree were observed in six patients.

Discussion

The results of this study show that 88% of the biopsies were completed successfully using EMLA cream, and additional analgesia was required in only two women. The first patient experienced pain when biopsied in the hair-bearing area. This occurred probably because trapping of cream within the hair prevented adequate skin absorption. This problem was overcome in other patients by trimming the hair with scissors; shaving was not necessary. In patient no. 10, a 2-cm epidermoid cyst was excised. Effective superficial analgesia was achieved but dissection from the underlying tissues to which the cyst was firmly adherent proved too painful as deep penetration of the cream through the cyst contents probably did not occur. However, additional infiltration caused only minimal discomfort. Two patients who had previously undergone the same procedure using local infiltration said they much preferred the topical application of the cream.

No severe side-effects were observed. The local reactions recorded were not clinically important and required no treatment. The main disadvantage of using the cream is the time required to achieve effective analgesia. However, although an application time of 60 min is recommended for skin (Wahlstedt *et al.* 1984), we found effective analgesia in the genital mucosal area after about 16 min. Where keratinized skin or thickened lesions are to be sampled the application time needs to be increased accordingly. Patients could be instructed to apply the cream before attending the clinic.

In conclusion, EMLA cream proved to be effective in achieving the necessary analgesia required to perform punch biopsies of the vulval skin. In combination with infiltration it enables more extensive skin surgery to be performed. Furthermore, fear is reduced and this in turn encourages the return of those who need long-term follow-up and repeated biopsies, for example patients with VIN.

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Low maternal serum alpha-fetoprotein at 10 weeks gestation and fetal Down's syndrome

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The acceptability of screening methods based upon the inverse relation of maternal serum alpha-fetoprotein (AFP) concentration at 15 weeks and Down's syndrome (Merkatz *et al.* 1984; Cuckle *et al.* 1984; Editorial 1985) would be greatly improved if the distribution of AFP concentrations in the first trimester of pregnancy were similar to that at 16 weeks. Reports by Brambati *et al.* (1986) and Barkai *et al.* (1987) suggest that this might well be the case and our own preliminary experience points in that direction.

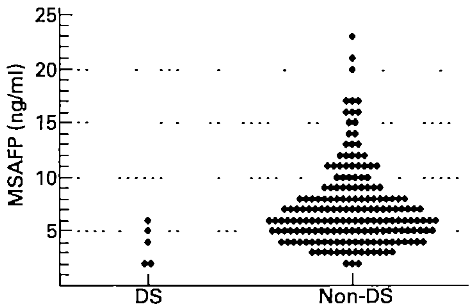

Fig. 1. Distribution of maternal serum alpha-fetoprotein (MSAFP) levels at 10 weeks gestation in pregnancies affected by fetal Down's syndrome (DS) and in pregnancies not affected (Non-DS). The multiples of the median of the affected pregnancies were 1·0, 0·8, 0·65, 0·3 and 0·3 respectively.

We collected blood samples just before chorionic villus sampling (CVS) around 10 weeks gestation from 188 women at increased risk for fetal chromosomal disorder and measured AFP concentrations using the AFP-EIA monoclonal kit from Abbott. Figure 1 shows the distribution of AFP levels in five women with fetal Down's syndrome and in 183 women without fetal Down's syndrome. All values of the affected pregnancies were at or below the median.

Maternal serum AFP levels in the affected pregnancies were significantly lower than in the unaffected pregnancies.

The use of maternal serum AFP at 15 weeks to screen for Down's syndrome has been advocated not only to select young women at a risk comparable with that of advanced maternal age (Cuckle *et al.* 1984), but also to identify older women at a risk lower than that based on age alone. Tabor *et al.* (1987) suggested the combination of maternal serum AFP levels and maternal age in iso-risk curves applicable to all pregnant women, irrespective of their age. They calculated that the diagnostic efficacy of amniocentesis for Down's syndrome increased from 28% when based on maternal age alone (≥35 years) to 53% when based on a ≥1:400 iso-risk curve for all pregnant women in Denmark. This looks attractive because the specificity only falls from 0·93 to 0·91, and the extra numbers of amniocenteses required are still manageable (from 6·9% to 9·4% of all pregnant women). However, the disadvantages of such screening relatively late in pregnancy are evident. A risk identified at that gestational age is harder to cope with than a risk known before or early in pregnancy, and the long wait for the results of amniocentesis increases parental anxiety. A screening method based on first trimester maternal serum AFP values would be a great advantage, as an addition to other screening tests done at first antenatal visit. Furthermore, it could be followed by a confirmative CVS, giving a result in a matter of days.

Our first results suggest that maternal serum AFP measurements in the first trimester may provide a useful screening test for Down's syndrome, possibly as good as AFP measurements in the 16th week and probably better in terms of acceptability.

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CORRESPONDENCE

Oral conception. Impregnation via the proximal gastrointestinal tract in a patient with an aplastic distal vagina

Dear Sir,

The report by Dr Verkuyl on oral conception [*Br J Obstet Gynaecol* (1988) **95,** 933–934] was most interesting. His patient had become pregnant, despite the absence of a vagina, through semen migrating across the abdomen space following puncture of the stomach wall with a knife, shortly after she had engaged in oral intercourse.

A similar episode was reported previously in the *American Medical Weekly* for 17 November 1874 by L. G. Capers and was noted by the *Lancet* (1875). This reported a bullet fired in the American Civil War, which on 12 May 1863 was said to have carried away the left testis of a soldier. This same bullet went on to penetrate the left side of a young woman nursing the injured nearby, and 278 days later she went into labour and gave birth to an 8-lb male infant. The hymen was intact and she was adamant that she was virginal. The infant was later operated upon and a malformed bullet was removed from a swelling in his scrotum. The soldier and mother were later reunited more formally, married and eventually produced three children by more routine methods.

Whilst it is known that 'capacitation' of semen is facilitated by many body fluids, including peritoneal fluid, it would appear that the calcium ion influx, which promotes acrosome reactivity, is not inhibited by acceleration or the very low pH of gastric hydrochloric acid.

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Fetal supraventricular tachycardia: detection by routine auscultation and successful in-utero management

Dear Sir,

I read with interest the case report by Macphail & Walkinshaw [*Br J Obstet Gynaecol* (1988) **95,** 1073–1076] on the use of flecainide to treat fetal supraventricular tachycardia.

Readers may be interested in a further case of in-utero treatment of a fetal supraventricular tachycardia. A 24-year-old woman in her second pregnancy was found to have a fetal tachycardia of 240 bt/min on routine auscultation by her general practitioner; this was shown to be a supraventricular tachycardia by M-mode echocardiography. Despite digitalization for 10 days (maternal serum level of 2 µg), the arrhythmia persisted. Real-time scanning showed a small pericardial effusion together with a minor degree of ascites.

Verapamil was given orally, 80 mg three times daily, increasing to 120 mg three times daily after 5 days, to give a maternal serum level of 80 ng/ml. At this stage the fetal tachycardia settled to 120 bt/min. A repeat scan 6 days later showed no evidence of ascites or pericardial effusion. There was no recurrence of the fetal tachycardia. Labour was induced by amniotomy at 38 weeks. A male infant weighing 3350 g was born vaginally in good condition. The baby was digitalized for 10 days and has had no arrythmias subsequently.

The use of verapamil would appear to have been a success for treating the fetal supraventricular tachycardia and mild degree of heart failure in this patient. It should, however, be avoided in the presence of advanced hydrops as, being a negative inotropic agent, fetal outcome could be further compromised (Wladimiroff & Stewart 1985). Whilst the lowest dosage should be used to restore sinus rhythm, maternal serum levels usually need to be in the upper part of the therapeutic range (50–100 ng/ml) as fetal levels are 25–50% of maternal levels

Routine antenatal auscultation remains a useful screening tool, even in the presence of normal fetal movements.

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BOOK REVIEWS

Diabetes Mellitus in Pregnancy: Principles and Practice by E. Albert Reece & Donald R. Coustan. Churchill Livingstone, Edinburgh, 1988, 651 pages with figures and tables, £65.00

This book is a welcome addition to the available publications on pregnancy complicated by diabetes.

All but three of the contributors are based in the USA, but this has not produced any obvious bias as the European literature is fully reviewed.

The book starts with a tribute to Priscilla White, then progresses through 31 chapters in 10 sections. The first, on general medical considerations, contains excellent reviews of diabetes epidemiology, carbohydrate metabolism in the non-pregnant, and the psychological changes induced by pregnancy. There are five comprehensive chapters in the section on fetus and placenta.

In the section on the management of carbohydrate intolerance in pregnancy, insulin treatment and the dietary contributions to control are taken in separate chapters. Whilst the logic of this is clear it does seem to me to encourage doctors to think in compartments instead of integrating methods of control. A surprisingly long contribution on exercise in pregnancy perhaps reflects current American concerns. The chapter on ultrasound in the management of the diabetic pregnancy takes an appropriately critical view of the concept of 'early growth delay'. The chapter on Doppler ultrasonography seems out of proportion to its current place in the management of the pregnant diabetic.

In the section on gestational diabetes there is a suitably guarded assessment of the tests available to make this diagnosis. Coustan, one of the editors, contributes an excellent chapter on management of gestational diabetes, in which he reports the extension of his non-randomized studies of the management of this condition. He speculates that serial amniotic fluid insulin measurements as a diagnostic marker for fetal hyperinsulinism may become a means of targeting treatment on the high-risk case. Cousins contributes a fascinating chapter on the frequency of obstetric complications based on a 20-year systematic literature review. The chapter on retinopathy is accompanied by an excellent series of retinal photographs and fluorescein angiograms.

Coustan's chapter on timing of delivery highlights the uncertainty in this area with a recommendation to deliver electively at 38 weeks with a favourable cervix but to delay delivery if the cervix is unfavourable. It is hard to know what the relation of cervical favourability to the risk of intrauterine death might be.

The excellent chapter on long-term outcome of infants of diabetic mothers is very welcome.

For those with a special interest in the management of pregnancy complicated by diabetes I would recommend a personal copy. This book should certainly be on the shelves of the medical library in every unit where physicians, obstetricians and neonatologists share the care of diabetic women in pregnancy.

R. B. Fraser

Books received some of which may be reviewed at a later date

A New Kind of Doctor by Julian Tudor Hart. Merlin Press, London, 1988, 362 pages, £12.95

Ultrasonography in Obstetrics and Gynecology Second Edition edited by Peter W. Callen. W. B. Saunders Company, Philadelphia, London, 1988, 496 pages fully illustrated, £40.00

The Developing Human: Clinically Orientated Embryology Fourth edition by Keith L. Moore. W. B. Saunders Company, 1988, 462 pages fully illustrated, £18.95

Drugs, Alcohol, Pregnancy and Parenting edited by Ira J. Chasnoff. Kluwer Academic Publishers, Dordrecht, Boston, London, 1988, 206 pages with figures and tables, £25.00, Dfl 99, US $44.50

Complications of Gynecologic and Obstetric Management edited by Michael Newton &

Edward R. Newton. W. B. Saunders Co., Philadelphia, London, 1988, 548 pages with figures and tables, £34.95

Doppler Ultrasound: Physics, Instrumentation and Clinical Applications by D. H. Evans, W. N. McDickens, R. Skidmore & J. P. Woodcock. John Wiley & Sons, Chichester, New York, 1989, 297 pages with figures and tables, £47.50

Controversies in Urology edited by C. Eugene Carlton Jr. Year Book Medical Publishers, Inc., Chicago, London, Boca Raton, 1988, 358 pages with figures and tables, £43.00

Picture Tests in Embryology by Marjorie A. England. Wolfe Medical Publications Ltd, 1989, 128 pages fully illustrated with colour plates, £7.50

A Colour Atlas of Gynaecological Surgery: Abdominal Operations for Benign Conditions Volume 2 Revised edition by David H. Lees & Albert Singer. Wolfe Medical Publications Ltd, London, 1989, 288 pages fully illustrated with colour plates, £70.00

Fetal Neurology (The International Review of Child Neurology) edited by Alan Hill & Joseph J. Volpe. Raven Press, New York, 1989, 303 pages with figures and tables, $86.50

Cervical Cancer by Jane Chomet & Julian Chomet. Grapevine, Thorsons Publishing Group, Wellingborough, 1989, 192 pages, £4.99 paperback original

Anorectal Malformations in Children: Update 1988 (March of Dimes Birth Defects Foundation Birth Defects: Original Article Series, Vol. 24, No. 4, 1988) edited by F. Douglas Stephens & E. Durham Smith. Alan R. Liss, New York, 1988, 620 pages, $150.00

Baillière's Clinical Obstetrics and Gynaecology. International Practice and Research. Antenatal and Perinatal Causes of Handicap. Vol. 2, No. 1, March 1988 edited by N. Patel. Baillière Tindall, London, Philadelphia, 1988, 240 pages, annual subscription £35.00 post free, single issue £15.00 post free

Human Reproduction and In Vitro Fertilisation by Henry Leese. Macmillan Education Ltd, Basingstoke, 1989, 120 pages, £5.95 paperback only

Common Gynaecological Emergencies by J. M. Monaghan & D. Ireland. Wright, Sevenoaks, 1988, 151 pages, £8.95

The 1988 Year Book of Perinatal and Neonatal Medicine edited by Marshall H. Klaus & Avroy A. Fanaroff. Year Book Medical Publishers, Inc., Chicago, London, Boca Raton, 1988, 344 pages, £33.00

The 1988 Year Book of Urology edited by Jay Y. Gillenwater & Stuart S. Howards. Year Book Medical Publishers, Inc., Chicago, London, Boca Raton, 309 pages, £35.50

World Health Statistics. Vol. 41, No. 3/4, 1988 World Health Organization, Geneva, Sw.Fr. 23

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COMMENTARIES

The obstetric vacuum extractor is the instrument of first choice for operative vaginal delivery

Thirty years have passed since Malmstrom's obstetric vacuum extractor was first used in Britain (Chalmers 1960). Although the vacuum extractor has more or less replaced forceps in most other parts of Europe, only a small minority of obstetricians in Britain, North America and Australasia use this instrument at all, let alone as the instrument of first choice for assisted vaginal delivery (Chalmers & Richards 1977; Bergsjø *et al.* 1983; Vacca *et al.* 1983).

Outsiders looking in on our speciality must regard it as somewhat bizarre that the instrument selected to assist a woman to give birth vaginally apparently depends more on the language spoken by her obstetrician than anything else. They might justifiably go on to ask what efforts the profession has made to assess the relative merits of vacuum extraction and forceps delivery. After all, millions of women worldwide require instrumental vaginal delivery each year. Thus, even if the advantages of one instrument over the other are quite modest, very large numbers of women and babies might benefit if whichever instrument was shown to be inferior was used less extensively.

There are some circumstances in which either forceps delivery or vacuum extraction is clearly preferable. When assistance is required for the birth of a baby presenting by the face, for example, forceps delivery represents the only alternative to caesarean section; similarly, vacuum extraction may be invaluable in assisting the birth of the second of twins. But which of the two instruments should be the instrument of first choice for the vast majority of assisted vaginal deliveries?

In this issue of the Journal, Johanson *et al.* (p. 537) report a randomized comparison of vacuum extraction (using a silicone rubber cup) and forceps delivery. Their results confirm the findings of previous randomized comparisons of the two instruments (Lasbrey *et al.* 1964; Vacca *et al.* 1983; Dell *et al.* 1985) that selection of the vacuum extractor as the instrument of first choice for operative vaginal delivery results in a substantial reduction in maternal morbidity.

Extrapolation of the data derived from the trial reported by Johanson *et al.* in this issue (p. 537) and the other trial conducted in Britain (Vacca *et al.* 1983) yields some important estimates of the costs to women of the continued preference for forceps in this country. Assuming that about 50 000 women will require instrumental vaginal delivery every year, the continued use of forceps as the instrument of first choice results, every year, in about 12 000 unnecessary pudendal blocks and other forms of regional anaesthesia for delivery, about 10 000 women unnecessarily experiencing moderate or severe pain during childbirth, 5000 more women with severe perineal or vaginal trauma than there need be, and 3500 women suffering unnecessarily from severe pain for several days after delivery.

The only justification for accepting preventable maternal morbidity on this scale would be good evidence that forceps as the instrument of first choice had some compensating advantages for either women or their babies. So far, no evidence of such an advantage has been detected in the available controlled comparisons, in spite of the fact that, on balance, the operators in these studies actually had more experience in the use of forceps than in the use of the vacuum extractor. Departments of obstetrics in which forceps remain the instrument of first choice must consider their position in the light of this evidence. If they believe that some important advantage of retaining forceps as the instrument of first choice remains undetected, they should conduct the randomized controlled trials required to test their as yet unsupported hypotheses.

The evidence that is already available should, however, prompt many departments of obstetrics to consider how best to substitute vacuum extraction for forceps delivery as the method of first choice for assisted vaginal delivery. Obstetricians in such departments will find another paper in this issue of the Journal relevant. Cohn *et al.* (p. 545) report a multicentre randomized comparison of a silicone rubber cup and the more widely used metal cups for vacuum extraction. The results of the study suggest that those departments wishing to increase their use of vacuum extraction should consider using silicone rubber cups: they can be applied rapidly and easily, and there is some evidence that they are less likely to cause scalp trauma than metal cups. Although failure to achieve delivery with the chosen instrument was low in both of the groups studied, failure was slightly more common when silicone rubber cups were selected. It is thus possible that metal cups may be preferable when difficulty during delivery is anticipated, and particular consideration should be given to the use of the Bird posterior cup when the head is malrotated (Vacca & Keirse 1989).

Replacing forceps with the vacuum extractor as the instrument of first choice for operative vaginal delivery will require appropriate training of obstetric and midwifery staff by those who are already familiar with the instrument. Needless to say, trainees (whatever their seniority) should begin to become familiar with vacuum extraction by using it when the fetal head is low and rotated anteriorly. In addition, greater attention than is usual must be paid to maintaining the equipment for vacuum extraction in good working order. Silicone rubber cups may offer some advantages in this respect because they are made in one piece, and are therefore less subject to air leaks. In a previous issue of the journal Constantine *et al.* (1989) showed how the central piped vacuum systems that are available in many hospitals, and the suction machines that should be available in every hospital for anaesthetic or operating theatre purposes, can be used as practical alternatives to the hand pumps and dedicated electric pumps that are usually used to create the vacuum required for vacuum extraction.

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Prophylactic oophorectomy

The debate concerning the removal of normal ovaries has been with us from the end of the 19th century when Lawson Tait, 'the foremost advocate of spaying in women' and Spencer Wells slugged out their acrimonious differences in the columns of the medical journals. Even surgeons who removed benign ovarian cysts were stigmatized as 'gelders' with devastating effects upon reputation. Nevertheless the 'extirpation of functionally active ovaries' was performed for pelvic pain, menorrhagia and the quaint Victorian defects of nymphomania and menstrual epileptic mania. Tait's operation, as it was now called, was received into the 20th century without enthusiasm and subsequently generations of gynaecologists have accepted that as only 0·2% of conserved ovaries become malignant it was inappropriate practice to remove them at the time of hysterectomy. Removal of 500 pairs of normal ovaries in order to save one cancer did not seem to be an attractive bargain.

The important questionnaire describing the practice of Fellows and Members of the Royal College of Obstetricians and Gynaecologists conducted by Jacobs & Oram, published in this issue (p.510), confirms that the removal of ovaries in the premenopausal woman at the time of abdominal hysterectomy remains an unpopular practice with only 24% of gynaecologists willing to remove ovaries in women aged 45–49 years and 59% in women aged ⩾49 years. It is notable that 85% would remove the ovaries if the woman were postmenopausal. The menopause is perceived to be a more important arbiter than age.

Can it be that such a large majority of gynaecologists are wrong about the value of prophylactic oophorectomy? The short-term symptoms and the long-term metabolic sequelae of the surgical menopause (Chakravarti *et al.* 1977), such as osteoporosis and an increased occurrence of heart attacks, are not disputed but it is arguable that replacement of oestrogens will overcome all of the problems of this iatrogenic endocrinopathy (Studd *et al.* 1986) and that the advantages of prophylactic oophorectomy in conjunction with modern hormone replacement therapy are considerable.

In spite of modern screening methods, hugely expensive radical surgery and toxic chemotherapy, the cure rate for ovarian cancer has been unchanged for the last 30 years with the overall 5-year survival of only 25%. Ovarian cancer still kills 4000 women per year; more than succumb to cervical cancer. The potential for prevention of ovarian cancer by prophylactic oophorectomy may be considerable.

The basic error of the cancer risk/benefit analysis is that the estimate of a 0·2% prospective cancer risk based on many papers including Randall *et al.* (1962) and others summarized by Jacobs & Oram (1987) is invalid because a large cohort of women has not been studied until death. This prospective risk is nothing more than a guess! On the other hand, it is easy to determine which women with ovarian cancer had previously had a hysterectomy or similar pelvic surgery when the ovaries could have been removed. From many studies it is clear that between 7% and 15% of patients could have been saved from subsequent ovarian carcinoma by a prophylactic oophorectomy (Bloom 1962; Gibbs 1971). Jacobs & Oram (1987) suggest that the figure is at least 10%. This added element of long-term protection from cancer could be achieved at no extra surgical time, risk or morbidity.

It is true that there are reports of advanced pelvic carcinoma of ovarian type occurring after prophylactic oophorectomy in high-risk ovarian cancer families but these examples are so rare that they do not invalidate any value that there may be in this argument.

There are also frequent benign complications following ovarian conservation that could be prevented by prophylactic oophorectomy. The development of cystic ovarian changes and periovarian adhesions in the form of the residual ovary syndrome occurs in 7% to 20% of women after hysterectomy (Randall 1963). The risk is greater in patients having a hysterectomy for pelvic inflammatory disease, endometriosis or pelvic pain. If apparently normal ovaries are preserved at the time of hysterectomy for endometriosis, the chances of further surgery for pelvic pain are 47% (Montgomery & Studd 1987). The chronic disabling, often cyclical, pain of the residual ovary syndrome frequently passes undiagnosed and when eventually surgery is undertaken it is a procedure with attendant surgical risks of urinary tract injury greatly in excess of those of the initial hysterectomy.

The ageing of conserved ovaries allows the insidious appearance of the cyclical symptoms of depression, irritability and mastalgia that are characteristic of the premenstrual syndrome, and also the cyclical headache which corresponds to menstrual migraine. There is no menstruation to aid the diagnosis but these cyclical symptoms of ovarian activity, best called the 'ovarian cycle syndrome', increase with age and are at their worst in the few years before ovarian failure (Magos 1988). As there is only recent awareness of this syndrome it is not yet possible to assess the prevalence but it is presumably as common as premenstrual tension in this age group. The diagnosis is usually missed by psychiatrists and gynaecologists alike who do not recognize the cyclical nature of these hormone-responsive psychiatric symptoms.

Not only is the 'ovarian cycle syndrome' unrecognized because there is no menstruation, but climacteric symptoms are not considered because the woman still has ovaries although they may fail prematurely after hysterectomy. Siddle *et al.* (1987) demonstrated that the age of ovarian failure was 4 years earlier in women after hysterectomy compared with the age of the natural menopause and that 34% of women developed ovarian failure and climacteric symptoms within 2 years of surgery. This premature ovarian failure occurred as commonly in the younger woman as in the older, perimenopausal woman. The cause is obscure but may be related to decreased ovarian blood supply or perhaps a loss of endometrial endocrine activity.

Even without hysterectomy the ovaries normally begin to fail from the age of 40. This is clearly shown by the loss of fertility, decreasing plasma oestrogen levels, the occurrence of climacteric symptoms before the cessation of periods and the decline in vertebral bone density from the peak bone mass found at the age of 40. Prophylactic oophorectomy prevents the complacent attitude that conserved ovaries remain functional and allows, indeed demands, prompt and effective hormone replacement therapy at the time when it is clearly required.

The instinctive objection to prophylactic oophorectomy is that normal ovaries (like normal breasts and normal testes) need not be removed as most people wish to live out their days as intact as possible. There is no doubt that this view, keenly held by most women and gynaecologists alike, will and should prevail until there is convincing evidence that ovarian conservation is unsafe.

Other objections to oophorectomy concern the efficacy, the safety and the availability of hormone replacement therapy. There is now good evidence that oestrogen replacement therapy prevents the onset of osteoporosis (Savvas *et al.* 1988), reduces the occurrence of heart disease (Ross *et al.* 1981), reduces the frequency of strokes (Paganini-Hill *et al.* 1988) and is effective in abolishing a whole range of climacteric symptoms (Brincat *et al.* 1984; Studd *et al.* 1986). Fears about safety persist but are unjustified because oestrogen therapy is certainly safer than residual ovaries with their inherent potential for disease. There remains some anxiety about the danger of breast cancer but generally the data are reassuring on this point. The only clear obstacles to oestrogen therapy are the need for a withdrawal bleed and the need for cyclical progestogens (Studd & Whitehead 1988). These side-effects only apply to women who have a uterus and are thus irrelevant to this issue.

The problem of availability of hormone replacement therapy is a valid concern as the logistics of treating large numbers of prematurely menopausal women with replacement oestrogens may not be simple. The initial therapy of leaving pellets of oestradiol, and perhaps also testosterone, in the wound on closure is straightforward but already many routine gynaecological clinics are being overwhelmed by patients attending for repeat hormone implants. It is clearly no worthwhile achievement for gynaecologists to create a surgical oestrogen deficiency state and then not to have the facilities to treat it adequately.

There are many good arguments for prophylactic oophorectomy at the time of hysterectomy in premenopausal women with the guarantee of long-term oral or percutaneous oestrogen therapy. Prophylactic oophorectomy should be offered to all women over the age of 40 having an abdominal hysterectomy but should only be performed after adequate discussion, understanding and of course consent. The woman has the ultimate choice. If she exercises what is perhaps the only worthwhile argument against prophylactic oophorectomy, namely a sentimental desire to keep her ovaries, then it would be a foolish and insensitive gynaecologist who ignores this compelling argument.

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Prevention of ovarian cancer: a survey of the practice of prophylactic oophorectomy by fellows and members of the Royal College of Obstetricians and Gynaecologists

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Summary. A questionnaire designed to investigate attitudes to prophylactic oophorectomy was sent to 2817 fellows and members of the Royal College of Obstetricians and Gynaecologists. A total of 1142 replies was received from those who performed regular sessions of gynaecological surgery. The number of respondents who said they would usually remove apparently normal ovaries at the time of abdominal hysterectomy from premenopausal women in age groups 35–39, 40–44, 45–49 and over 49 years was 4 (0·4%), 27 (2%), 234 (20%) and 585 (51%) respectively, and from postmenopausal women 974 (85%). The majority of respondents said that (i) they would prescribe hormone replacement therapy in oophorectomized premenopausal women (82%); (ii) they did not consider unilateral oophorectomy to have a role in prevention of ovarian cancer (84%); and (iii) they routinely discussed the question of prophylactic oophorectomy with their patients before operation (65%). Only 128 (11%) of the respondents believed that $\geqslant$10% of ovarian cancers in the UK could be prevented by prophylactic oophorectomy at the time of operation for benign disease, and 505 (44%) would perform prophylactic oophorectomy as a primary surgical procedure in women who had a strong family history of ovarian cancer.

Ovarian cancer is a disease which presents late and responds poorly to treatment. In spite of intensive efforts to improve the therapy of established disease with advances in surgical and chemotherapeutic techniques, the prognosis for ovarian cancer has remained largely unchanged for 30 years. The overall 5-year survival for patients with disease outside the ovary at initial surgery is only 15% (Kottmeier 1982). Unfortunately, over 75% of patients fall within this group. Attempts to detect early localized ovarian cancer have not yet been successful although studies using the CA 125 radioimmunoassay and ultrasonography are currently underway at The London Hospital (Jacobs *et al.* 1988) and Kings College Hospital (Campbell *et al.* 1982; Goswamy *et al.* 1983)

Oophorectomy remains the only available method for prevention of ovarian cancer. Variation in the performance of prophylactic oophorectomy by gynaecologists and general surgeons is, however, extreme and there are no generally accepted criteria for the removal or conservation of the apparently normal ovary.

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This wide divergence in clinical practice reflects the lack of reliable data concerning the consequences, both beneficial and otherwise, of bilateral oophorectomy.

We therefore set out to investigate attitudes to prophylactic oophorectomy and its basis among practising gynaecologists in the British Isles.

Materials and methods

The questionnaire shown in Table 1 was sent by post to 2817 fellows and members of the RCOG resident in the British Isles using address labels provided by the RCOG following approval by its Scientific Advisory Committee. The questionnaire was on a self-sealing card and reply postage was paid by freepost. The replies received from fellows and members with a regular session of gynaecological surgery were analysed statistically using the χ^2-test with Yates' correction.

Results

Of 2817 questionnaires sent out, 1356 replies were received; an overall response rate of 48%. Figure 1 summarizes the grade (NHS grade or academic equivalent) of the fellows and members replying and the type of hospital in which they mostly operated. Overall, 214 of the replies were from members or fellows not performing a regular session of gynaecological surgery and these replies have been excluded from further analysis. The largest number of replies for a single year of membership was 86 (for 1986) and the longest duration of membership was from 1936.

The answers to each of the seven questions relating to prophylactic oophorectomy, as detailed in Table 1, were as follows.

Question 1. Only four of the 1142 (0·4%) respondents indicated that they would usually remove apparently normal ovaries from women aged 35–39 years undergoing abdominal hysterectomy for benign disease; 27 (2%) would do so for the age group 40–44 years; 234 (20%) for the age group 45–49; 585 (51%) for premenopausal women over 49 years; and 974 (85%) for postmenopausal women. Consultants were less likely than non-consultants to remove ovaries in premenopausal women aged 45–49 (20% compared with 28%, $P<0{\cdot}02$) and over 49 (50% compared with 62%, $P<0{\cdot}01$). Those admitted to the membership within the last 15 years were more likely than those admitted before 1972 to remove on a routine basis apparently normal ovaries in premenopausal women aged 45–49 (25% compared with 19%, $P<0{\cdot}05$) or over 49 (58% compared with 50%, $P<0{\cdot}02$) and postmenopausal women (91% compared with 85%, $P<0{\cdot}01$).

Question 2. When deciding whether or not to remove apparently normal ovaries, 667 respondents (58%) would be influenced by family history of gynaecological cancer, 711 (62%) by past history of breast cancer, 74 (6%) by parity and 35 (3%) by contraceptive history (Table 2).

Question 3. A total of 934 respondents (82%) said they would usually prescribe hormone replacement therapy when performing a prophylactic oophorectomy in a premenopausal woman; 468 orally, 334 by implant, and 132 either oral or implant therapy (Table 2). Those obtaining membership before 1962 were less likely to prescribe hormone replacement therapy than those obtaining membership in 1962 or later (72% compared with 88%, $P<0{\cdot}01$).

Question 4. Overall 960 respondents (84%) did not consider unilateral oophorectomy to have a role in the prevention of ovarian cancer (Table 2).

Question 5. Overall 747 respondents (65%) said that they routinely discussed the question of prophylactic oophorectomy with their patients before operation (Table 2). There were no significant differences according to grade and year of membership but those respondents who routinely discussed oophorectomy before operation were more likely to remove, on a routine basis, apparently normal ovaries at abdominal hysterectomy for benign disease in premenopausal women aged 40–44 (3·7% compared with 0·5%, $P<0{\cdot}01$), 45–49 (31% compared with 6%, $P<0{\cdot}01$) or over 49 (51% compared with 31%, $P<0{\cdot}01$) and postmenopausal women (93% compared with 79%, $P<0{\cdot}01$).

Question 6. Of the 1142 respondents 64 (6%) believed that <1% of ovarian cancers could be prevented by prophylactic oophorectomy at the time of operation for benign disease; 590 (52%) considered that ≤5% could be prevented and 764 (67%) thought the proportion was ≤10%.

Table 1. Questionnaire about prophylactic oophorectomy sent to 2817 fellows and members of the RCOG

(A) Grade (or NHS equivalent)
[ ] Consultant [ ] Senior Registrar [ ] Registrar [ ] GP [ ] Other (specify)

(B) Do you have a regular session of gynaecological surgery? [ ] Yes [ ] No
If NO do not complete the rest of the questionnaire but please post this card.

(C) Is the majority of your gynaecological surgery performed in a:
[ ] Teaching hospital [ ] District general hospital [ ] Other (specify)

(D) Year of membership RCOG [19]

(1) When performing an abdominal hysterectomy for benign disease is it your ususal practice to remove apparently normal ovaries in:

	Yes	No
Premenopausal women aged 35–39 years	[ ]	[ ]
Premenopausal women aged 40–44 years	[ ]	[ ]
Premenopausal women aged 45–49 years	[ ]	[ ]
Premenopausal women aged over 49 years	[ ]	[ ]
Postmenopausal women	[ ]	[ ]

(2) When deciding whether or not to remove apparently normal ovaries is your decision influenced by the following factors?

	Yes	No
Family history of gynaecological cancer	[ ]	[ ]
Past history of breast cancer	[ ]	[ ]
Parity	[ ]	[ ]
Contraceptive practice	[ ]	[ ]

(3) When you perform a prophylactic oophorectomy in a premenopausal woman is it your usual practice to prescribe hormone replacement therapy?

No [ ] Yes, oral [ ] Yes, implant [ ]

	Yes	No
(4) Do you consider *unilateral oophorectomy* to have a role in prevention of ovarian cancer?	[ ]	[ ]
(5) Do you routinely discuss the question of prophylactic oophorectomy with your patients pre-operatively?	[ ]	[ ]

(6) What percentage of ovarian cancers in the UK do you think could be prevented by prophylactic oophorectomy at the time of operation for benign disease? [%]

	Yes	No
(7) Would you perform prophylactic oophorectomy as a primary surgical procedure in women with a strong family history of ovarian cancer?	[ ]	[ ]

Only 128 (11%) replied that >10% of ovarian cancers in the UK could be prevented, and 250 (22%) did not know the answer to this question.

Question 7. Overall 505 respondents (44%) said that they would perform prophylactic oophorectomy as a primary surgical procedure in women with a strong family history of ovarian cancer. Fellows and members at teaching hospitals were more likely to answer 'yes' to this question than other fellows and members (52% compared with 43%, $P<0{\cdot}01$).

Discussion

This questionnaire was designed to achieve as high a response rate as possible. For that reason reply cards were anonymous, the number of questions asked was limited to seven, and return postage was paid by freepost. Figures provided

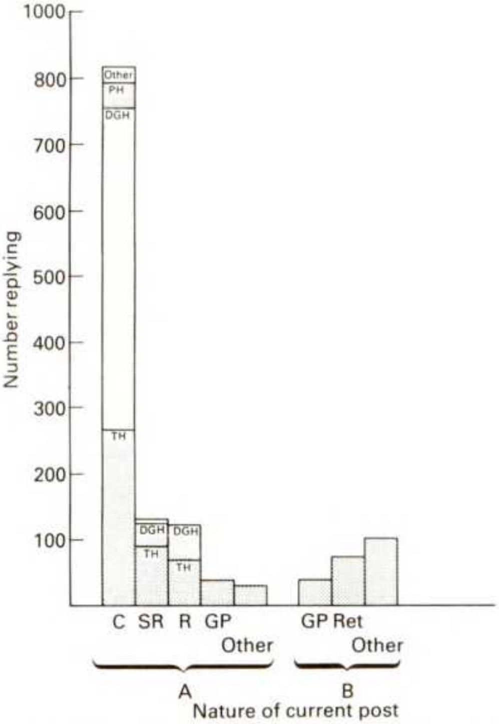

Fig. 1. Grade (NHS or academic equivalent) of 1356 fellows and members replying to the questionnaire, and type of hospital in which the majority of their surgery was performed. C, Consultant; SR, senior registrar; R, registrar; GP, general practitioner; PH, private hospital; DGH, district general hospital; TH, teaching hospital; Ret, retired. (A) Regular session of gynaecological surgery (1142). (B) No regular session of gynaecological surgery (214).

by the Departments of Health for Scotland, Northern Ireland, England and Wales (personal communication) indicate that on 1 August 1986 there were 933 consultant posts, 167 senior registrar posts and 603 registrar posts in obstetrics and gynaecology in the UK. On the basis of these figures, we estimate that although the overall response rate was only 48%, replies to this questionnaire were received from approximately 87% of consultants, 78% of senior registrars and 20% of registrars in the UK. The small proportion of registrars replying may reflect the fact that many have not obtained membership and that registrar staff have a relatively high mobility resulting in outdating of the College mailing list. The latter suggestion is supported by the finding that approximately 80% of those obtaining membership in 1986 responded, compared with about 40% of those obtaining membership in the previous 5 years.

Question 1 addressed the influence of age and menopausal status on the practice of prophylactic oophorectomy. As life expectancy for women in the UK is into the 8th decade, all women must be assumed to be at equal risk of reaching both the menopause and the high-risk age group for ovarian cancer. The answers to question 1 therefore indicate opinion as to when the risks of loss of ovarian function after prophylactic oophorectomy (which decrease with increasing age and after the menopause) are exceeded by the lifetime risk of developing ovarian cancer (which is a constant for each individual). There was overwhelming agreement that between the ages of 35 and 44 the balance is heavily in favour of ovarian conservation. It was equally clear that most fellows and members felt the balance had swung towards oophorectomy when considering postmenopausal women. However, opinion was divided concerning premenopausal women over 45 years. Surprisingly, 389 respondents (34%) would perform a prophylactic oophorectomy on a postmenopausal woman but not on a premenopausal woman over 49 years of age under-

Table 2. Answers to questions 2, 3, 4, 5 and 7 detailed in Table 1

	Answers (n=1142)				
	Yes		No		No response
Question	n	(%)	n	(%)	n
2. Family history of gynaecological cancer	667	(58·4)	450	(39·4)	25
2. Past history of breast cancer	711	(62·3)	408	(35·7)	23
2. Parity	74	(6·5)	1036	(90·7)	32
2. Contraceptive practice	35	(3·1)	1073	(94·0)	34
3. Prescription of hormone replacement therapy	934	(81·8)	153	(13·4)	55
4. Unilateral oophorectomy	150	(13·1)	960	(84·1)	32
5. Routine discussion	747	(65·4)	386	(33·8)	9
7. Primary surgical procedure	505	(44·2)	574	(50·3)	63

Table 3. Answers to question 6 (Table 1) given by 1142 respondents

Percentage of ovarian cancers in the UK preventable by oophorectomy	Respondents *n*	(%)
<1	64	(5·6)
1– 5	526	(46·1)
6–10	174	(15·2)
11–15	26	(2·3)
16–20	36	(3·2)
21–25	11	(1·0)
26–30	19	(1·7)
>30	36	(3·2)
No response	250	(21·9)

going the same operation. Clearly the division between premenopausal and postmenopausal status is regarded as important, independent of age.

A majority of fellows and members would consider a family history of gynaecological cancer and a past history of breast cancer when making a decision concerning prophylactic oophorectomy (question 2). Only a small minority would consider parity and preceding contraceptive practice. Nulliparous women and women with a past history of breast cancer are at increased relative risk of developing ovarian cancer, the risk associated with a family history of ovarian cancer may be up to 18-fold, whilst the oral contraceptive pill is protective against ovarian cancer (Hildreth *et al.* 1981; Prior & Waterhouse 1981; Franceschi *et al.* 1982; Casagrande *et al.* 1979; Risch *et al.* 1983; La Vecchia *et al.* 1983; Booth 1986; Newhouse *et al.* 1977). Although these are only relative risk factors they are the best criteria available for assessing an individual's risk of developing ovarian cancer and it would seem logical to consider them when the question of prophylactic oophorectomy arises, even though there may be other reasons in an individual case for not acting on them.

Opinion was divided as to whether prophylactic oophorectomy should be performed as a primary surgical procedure in women with a strong family history of ovarian cancer. This problem arises rarely in clinical practice and although case-control studies have provided a theoretical basis for such operations (Hildreth *et al.* 1981; Franceschi *et al.* 1982), it remains difficult to advise surgery in apparently healthy women. There was overwhelming agreement that hormone replacement therapy should be prescribed following premenopausal oophorectomy. Interestingly those obtaining membership before 1962 were less likely to prescribe hormone replacement therapy. There is little information available concerning the role of unilateral oophorectomy in the prevention of ovarian cancer but 84% of fellows and members did not consider it valuable.

Published reports suggest that current oophorectomy rates reduce the occurrence of ovarian cancer by up to 12% (Howe 1984) and that a further 10–14% of ovarian cancers could be prevented by prophylactic oophorectomy at the time of operation for benign disease (Speert 1949; Golub 1953; Counsellor *et al.* 1955; Bloom 1962; Fagan *et al.* 1956; Terz *et al.* 1967; Gibb 1971; Kofler 1972; Grundsell *et al.* 1981). It is clear, therefore, that the correct answer to question 6 is at least 10% and may be as high as 25%. Only 128 respondents (11%) said that ≥10% of ovarian cancers could be prevented by prophylactic oophorectomy, and 250 (22%) were unable to answer this question. Those fellows and members answering 'correctly' (within broad limits >10%–<25%) were more likely than those giving 'incorrect' replies or not answering to remove ovaries at hysterectomy for benign disease in premenopausal women aged 45–49 (48% compared with 20%, $P<0\cdot01$) or over 49 years (75% compared with 52%, $P<0\cdot01$) and postmenopausal women (95% compared with 89%, $P<0\cdot05$). These findings suggest that the potential preventive role of oophorectomy is underestimated due to a lack of knowledge about this subject. As a consequence, oophorectomy as a preventive measure may not be considered in some women where it is appropriate, particularly in premenopausal women over 45 years of age.

The wide spectrum of opinion and practice revealed by some of the answers to the questions in this survey is a predictable consequence of the large gaps in our knowledge concerning the epidemiology of ovarian cancer, the consequences of early loss of ovarian function and the long-term efficacy of hormone replacement therapy. Whilst this lack of reliable data persists it is not possible to define correct or incorrect clinical practice. The individual patient's views on the subject remain the most important and final arbiter. It is, however, possible to reach conclusions on a number of points, in relation to current practice. The view of the majority of the fellows and members of the RCOG is that prophylactic oophorectomy should be performed at the time of operation for benign disease in postmenopausal women and that ovaries should be retained at similar operations in premenopausal women under 45 years of age Prophylactic oophorectomy in premenopausal women over 45 years of age remains controversial but should always be followed by hormone replacement therapy. The majority of fellows and members underestimated the proportion of ovarian cancers which could be prevented by prophylactic oophorectomy.

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Monoclonal antibodies and their usefulness in epithelial ovarian cancer. A review

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That cancer cells differ from normal cells qualitatively and quantitatively is well known. The oncogene–antioncogene theory of the basis of cancer gives the hope that tests which depend on the essential cancerousness of a cell rather than on its physical properties, demonstrated by imaging techniques which may be unreliable in recurrent ovarian cancer (Khan *et al.* 1983; Blaquiere & Husband 1983; Calkins *et al.* 1987), will lead to earlier diagnosis and more successful treatment. Levi *et al.* (1969) first identified a surface antigen on ovarian cancer cells which was not present on normal ovary, non-epithelial ovarian tumours or other tumours, including those of Mullerian origin. Subsequently, a number of high molecular weight muco- and glycoproteins, defined by xenogeneic polyclonic rabbit antiserum (Crowther 1979), were found to be present in the serum of patients with untreated ovarian cancer. Monoclonal antibody techniques have now been used to establish the presence of several different cell surface antigens in ovarian cancer including CA125 (Bast *et al.* 1983), placental alkaline phosphatase (PLAP) (Travers & Bodmer 1984; Davies *et al.* 1985*b*) and human milk fat globule antigen (HMFG) (Taylor-Papadimitriou *et al.* 1981). All of these may be found on other malignant cells and, in the case of HMFG, in normal epithelial tissue. Thus, this first generation of monoclonal antibodies has not yet realized the hope that tumour-specific antigens would be found with ease, but their use has encouraged further search. Monoclonal antibodies are used *in vitro* in the histological and cytological diagnosis of tumours and in serial measurements of serum tumour markers to aid the clinical management of patients. *In vivo*, they are being used routinely in the radioimmunolocalization of tumour deposits (radioimmunoscintigraphy) and, more recently, in their treatment (radioimmunotherapy).

Tissue diagnosis

The in-vitro binding of monoclonal antibodies to antigens in ovarian cancer tissue, as assessed by immunoperoxidase staining, varies between 56% for PLAP (Davies *et al.* 1985*b*) and 90% for HMFG (Ward 1986), but these can not be used diagnostically, as up to 25% of benign ovarian tumours also stain for PLAP (Davies *et al.* 1985*b*). This has led to the awareness that the normal ovarian cell surface mucoprotein is highly glycosylated, whereas the cancer cell mucoprotein is partly deglycosylated. A monoclonal antibody, SM3, has been developed specifically against the deglycosylated core mucoprotein which has much higher selectivity for the ovarian cancer cell (Burchell *et al.* 1987).

This approach is designed to help the cytologist identifying tissue from the patient presenting with disseminated intra-abdominal carcinomatosis of unknown primary, and in identifying malignant cells in serous effusions. Mesothelial cells may cause diagnostic confusion, but several monoclonal antibodies, including B 72.3 (Lastoria *et al.* 1988), do not react with these, but react well with epithelial cancer cells. Thus the use of a panel of monoclonal antibodies with different affinities for ovarian, breast or colonic carcinoma might aid diagnosis (Neville *et al.* 1982). Epenetos *et al.*

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(1982*b*) found only one false-positive result in a study of 27 patients with non-malignant serous effusions, and no sample with mesothelial cells stained positively.

'Borderline' tumours may also have qualitative differences in their cells which could predict malignant potential. Symonds *et al.* (1985) described a recurrent ovarian tumour which bound strongly to monoclonal antibody 791T/36. The original tumour had been classified as benign, but its recurrence as well as the antibody binding prompted review of the histology and it was reclassified as malignant.

Serological identification of tumour antigens

Elevated serum levels of CA125 and HMFG are found in 80–95% of patients with primary epithelial ovarian cancer (Bast *et al.* 1983; Ward 1986), but this does not differentiate ovarian cancer from other intra-abdominal malignancies or masses. CA125 is elevated in 50–60% of patients with pancreatic and gastrointestinal malignancies, in patients with fibroids and other non-malignant disorders (Bast *et al.* 1983). PLAP levels are raised in cigarette smokers (Davies *et al.* 1985*b*). Ovarian cancer antigen levels are elevated in 39% of patients with benign ovarian tumours (Tucker & Milton Ward 1987), so patients with abdominal masses will continue to require diagnostic laparotomy.

Could the determination of elevated serum marker levels be used as a screening test for ovarian cancer, or in the monitoring of patients during treatment? At present, the answer must be a qualified 'no' since none of these antigens is sufficiently specific to accurately mirror the disease state. Einhorn *et al.* (1987) could find no obvious benefit from screening over 1000 women in Sweden, 3.3% had elevated CA125 levels but none had ovarian cancer although four had benign gynaecological disease. Thus, the false-positive rates are too high for a screening test in women ≥40 years of age who are likely to have a significant number of non-malignant disorders.

In the monitoring of treatment, a fall in the serum level of a marker after surgical bulk reduction, followed by a rise during chemotherapy, correlates well with recurrent disease. However, persistently high marker levels may not necessarily imply progressive disease (e.g. CA125 may increase after radiotherapy). More importantly, low levels do not imply the absence of disease, and negative CA125 levels can occur in over 40% of women with small volume (<2 cm) or microscopic disease (Lambert 1987; Tucker & Milton Ward 1987). Ward (1986) found that 70% of patients with raised HMFG levels had persistent disease, but 29% of those in 'complete remission' also had raised levels. Perhaps a combined panel of more selective monoclonal antibodies might increase the degree of detection in small bulk disease.

Radioimmunoscintigraphy

This has developed from a research to a diagnostic tool (Epenetos *et al.* 1982*a*; Granowska *et al.* 1984*a,b*, 1986, 1988; Pateisky *et al.* 1985; Davies *et al.* 1985*a*; Symonds *et al.* 1985; Kalofonos & Epenetos 1987). The pros and cons of the technique are reviewed by Bradwell & Dykes (1988), Britton & Granowska (1988) and Grossman & Rosebrough (1988). A gamma camera is used to obtain serial images of the distribution and uptake of a radiolabelled monoclonal antibody injected intravenously. The quality of the image depends on the radionuclide used. Because it has a long half-life and low sensitivity, the use of I-131 is being abandoned in favour of In-111 and I-123, which have better characteristics for the gamma camera (Britton & Granowska 1987).

There is often heterogeneity of antigen expression by malignant cells, some may fail to complex with the monoclonal antibody, or there may be non-specific uptake by normal cells. The monoclonal antibody may separate from the radionuclide label. Computerized 'subtraction' of an initial image from one obtained 24 h later is often necessary to eradicate the background activity arising from uptake into the liver, general blood pool and bladder (Granowska *et al.* 1984*a*). Insufficient 'subtraction' increases the proportion of false-positive results, and lesions near areas of high background activity may be missed and contribute to false-negative results.

The first prospective radioimmunoscintigraphic study using I-123 labelled HMFG2 for the primary assessment of pelvic masses had a high false-positive rate because of uptake by other malignancies and benign ovarian cysts that are known to react with HMFG. A tubovarian abscess and a fibroid showed high blood pool activity. However, investigations in patients before second-look surgery demonstrated a sensitivity of 95%, with accurate localization of the ovarian cancer in 90% confirmed at surgery (Granowska *et al.* 1986).

Other reports, such as one by Symonds *et al* (1985) who used I-131 labelled monoclonal antibody 791T/36, confirm the lack of specificity for ovarian cancer when imaging a patient with a pelvic mass. Davies *et al.* (1985*a*), using an anti-PLAP antibody, identified focal ovarian deposits more easily than peritoneal seedlings, possibly reflecting the great heterogeneity of PLAP expression. Where an image is obtained, there is good correlation with the surgical findings. Therefore, although imaging can not diagnose a pelvic mass, the images obtained may help localize disease before second-look laparotomy and direct postoperative radiotherapy (Symonds *et al.* 1985).

Using a kinetic analysis and probability mapping in a biopsy-controlled prospective study, Granowska *et al.* (1988) have shown that radioimmunoscintigraphy can define small macroscopic or microscopic disease after chemotherapy, which is not detectable by standard radiological techniques. This procedure used in conjunction with serum markers might assist the assessment of patients for second-look surgery or changes in chemotherapy. A specific monoclonal antibody for the detection of small bulk disease would be a useful screening test in women at high risk of developing ovarian cancer, those with a strong family history (Tobacman *et al.* 1982) and those young women with colorectal carcinoma in whom prophylactic oophorectomy is not performed (Graffner *et al.* 1983). Kalofonos & Epenetos (1987) have recently reported on the use of OVLT3 which may well be totally ovarian specific.

The labelling of antibodies with technetium has now been achieved (Schwarz & Steinstraesser 1987), thus making this imaging technique available to all nuclear medicine departments. Furthermore, the isotope has other advantages of cheapness, safety and stability *in vivo* when bound to antibody.

Radioimmunotherapy

The intraperitoneal instillation of radiolabelled monclonal antibodies to 'target' radiotherapy to malignant deposits, introduced by the Hammersmith Oncology Group (1984), has its rationale in the natural pathology of this disease, as well as the pharmacokinetic advantage of intraperitoneal over intravenous drug administration (Dedrick *et al.* 1978). To date, 67 women have been treated in the UK. Patients had small intraperitoneal disease, often less than 2 cm, which had recurred after debulking surgery and chemotherapy. Most women experienced mild systemic upset, with vomiting, diarrhoea, myalgia and transient pyrexia, but there were some more serious complications. Ward *et al.* (1988) treated 11 women with 100–150 mCi (4–6 GBq) I-131 labelled HMFG2. Serious complications included two ileocutaneous fistulae. These were felt to be caused by radiation damage to the bowel rather than the disease itself, probably through location of the radiolabelled antibody on plaques of tumour on the bowel wall. Another patient developed severe thrombocytopenia when subsequently treated with carboplatin. Three patients could not be treated because of technical difficulties with leakage from the intraperitoneal catheter and infection (Crowther *et al.* 1989). Stewart *et al.* (1987, 1989) treated 36 women with a variety of monoclonal antibodies labelled with up to 150 mCi (5·5 GBq) 131-I. One patient developed a subphrenic abscess and another required a laparotomy for a perforated sigmoid colon. Several patients developed transient myelosuppression a month later, particularly if they had received more than 120 mCi (4·5 GBq).

Although this treatment is well tolerated, no substantial benefit has been shown for patients with small intraperitoneal disease. The only patients who may benefit are those with microscopic disease, or those whose troublesome ascites is palliated (Stewart *et al.* 1987, 1989). In those patients, the antigenic expression on ascitic cells may change (Ward *et al.* 1988). It is also necessary to check the in-vivo uptake of the antibody by radioimmunoscintigraphy. In one patient there was good uptake of the monoclonal antibody by the tissue *in vitro* but very poor uptake *in vivo* and therefore therapy was not given.

Stewart *et al.* (1989) have treated 18 women with yttrium-90 labelled monoclonal antibodies in doses of between 6 and 18 mCi (220–665 MBq). They have found no response in 7 of 8 patients and marrow toxicity at 1 month when the administered dose was over 12 mCi (450 MBq). We have treated one woman with macroscopic disease over 2 cm diameter by two separate doses of 10 mCi (320 MBq). There was a response initially only to the first dose, and another patient showed no response to this treatment.

The future

Monoclonal antibodies may bring exciting improvements in the fields of diagnosis and therapy in this usually fatal disease. At the present time, none of the tumour markers is sufficiently specific for serum levels or radioimmunolocalization to be helpful in diagnostic investigation of patients with abdominopelvic masses. However, in patients known to have ovarian cancer, serial measurements of serum markers and radioimmunoscintigraphic localization may help in diagnosing recurrence after or during treatment. Negative findings, unfortunately, do not indicate the absence of disease, although radioimmunoscintigraphy with computer-assisted kinetic analysis identified 3 of 4 true negatives, 75% (Granowska *et al.* 1988).

Radioimmunotherapy with monoclonal antibodies is in its infancy. The use of 'cocktails' of monoclonal antibodies each against an identified tumour antigen may enhance tumour uptake and overcome the problem of heterogeneity of antigen expression. A present constraint on exposing patients repeatedly to monoclonal antibodies is the development of anti-mouse antibodies and the possibility of serum sickness. The use of genetically engineered human monoclonal antibodies with murine active centres confined to the complementarity-determining regions (CDR) may obviate this problem (Riechmann *et al.* 1988). The toxicity from intraperitoneal radiolabelled monoclonal antibodies might be decreased and the tumoricidal dose increased, when labelled with pure beta-emitters such as 90-yttrium or 32-phosphorus compared with I-131, and ways of reducing the bone and marrow uptake are under consideration. It has been postulated (Oldham 1984) that tumours become resistant to chemotherapy because of inadequate delivery of the drug to necrotic areas, and low concentrations. Hence, one future possibility might be the postoperative intraperitoneal administration of monoclonal antibodies bound to cytotoxic drugs.

Radioimmunoscintigraphy involves many different disciplines: from the genetic engineering of the humanized antibody to radiolabelling with 99m-Technetium, routinely available in the nuclear medicine department, to computer-assisted kinetic and pattern analysis of the image. Each contribution can improve by a factor of 2 to 5. Radioimmunotherapy can build on these advances. In particular, various two-stage approaches are under active consideration which should enable intravenous therapy. An injection of a monoclonal antibody with double affinity, one for the tumour antigen and one for the radiotherapy agent, is injected first. It fixes to the tumour, but is cleared from the normal tissues over a period of time. The ligand containing the radiotherapy agent is then administered and binds to the antibody fixed to the tumour. This would improve the therapeutic ratio considerably and enable the subserosal deposits which are inaccessible to the intraperitoneal therapy (Ward *et al.* 1987) to be treated.

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Survival of younger cervical carcinoma patients treated by radical radiotherapy in the West of Scotland 1964–1984

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Summary. Between 1964 and 1984, 2011 patients in the West of Scotland were treated by radical radiotherapy for carcinoma of cervix. In keeping with the rise in incidence amongst younger patients nationally, the number of women aged <35 years seen during the 20-year period has doubled. Younger women (aged <35 or <45) have a better prognosis mainly because more present with earlier disease. Stage for stage there has been no change in survival of women of all ages treated by identical radiotherapy during this period. The rise in mortality of younger patients from carcinoma of cervix may be due to the increased incidence of the condition rather than a more virulent form of the disease.

Although overall mortality from carcinoma of cervix has declined steadily since the mid 1950s, the death rate amongst younger women has risen both in England and Wales and to a lesser extent in Scotland (Cook & Draper 1984). Cancer Registry data show that the incidence both of invasive and pre-invasive disease has also risen amongst younger women, but as these data are less complete than mortality statistics it is uncertain whether the increased death rate merely reflects an increase in the number of women with this disease or points to a poorer prognosis for younger women. It has been suggested that patients under 40 years of age have more aggressive and more lethal tumours, the 5-year survival of women with Stage IB disease being less than 50% (Ward *et al.* 1985) compared with a rate of over 80% usually quoted (Kottmeier 1982).

Whether or not younger women have a more lethal form of the disease is an important question as it is predicted that by the year 2000 the incidence of carcinoma of cervix will have risen by 50% in England and Wales and most of the predicted increase in incidence and mortality will occur in women <50 years of age (Beral & Booth 1986). Clearly these predictions have implications for treatment (Ward *et al.* 1985) and for the British screening programme, especially as the effectiveness of this programme has been repeatedly questioned (Editorial 1985; Draper & Cook 1983).

Conflicting results have appeared from Britain and elsewhere showing either increased survival for younger patients (Russell *et al.* 1987), decreased survival (Stanhope *et al.* 1980) or no change (Baltzer *et al.* 1982). We have examined the survival of over 2000 patients referred from a stable population resident in the West of Scotland treated over a 21-year period by the same radiotherapeutic techniques.

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During this period, patients fit for radical radiotherapy assigned to each FIGO stage were treated in the same way irrespective of age. Therefore any change in overall mortality or the death rate in each stage should be independent of treatment and should reflect a change in the natural history of the disease.

Subjects and methods

Between 1964 and 1984, 2011 patients suffering from invasive carcinoma of cervix were treated by radical radiotherapy at the Western Infirmary, Glasgow. This hospital is a major referral centre for the West of Scotland. There have been

Table 1. Carcinoma of cervix 1964–1984: presentation by stage and age group (percentage of total no. of women referred in each age group and time period)

Age group (years)	Stage	1964–67	1968–71	1972–75	1976–80	1981–84
<45	I	32·4	49·4	43·1	40·2	47·8
	II	39·0	27·1	27·7	31·0	17·8
	III+IV	28·6	23·6	29·2	28·7	34·4
	(*n*)	(105)	(85)	(65)	(87)	(90)
45–74	I	18·4	21·0	20·4	23·6	24·5
	II	41·0	33·1	38·2	36·3	31·3
	III+IV	40·6	45·8	41·4	40·1	44·2
	(*n*)	(354)	(323)	(285)	(284)	(248)

Table 2. Percentage surviving 5 years by age group and date of treatment (1964–1980)

	Age group (years)	1964–67	1968–71	1972–75	1976–80
Total no. of patients	<45	105	85	65	87
treated	45–74	354	323	285	284
Cumulative percentage	<45	62·7	63·0	67·6	59·4
surviving by age group	45–74	52·1	49·2	57·1	55·6
Overall χ^2 (1 d.f.) (controlling for stage)		0·38	0·25	0·43	0·88
P<		0·70	0·70	0·70	0·50
Death rate ratio*		0·895	0·906	0·854	1·197

*Ratio of observed to expected deaths in period (controlling for Stage) in the <45 age group, divided by the same ratio for those aged 45–74.

Table 3. Percentage surviving 5 years by age group and date of treatment (1964–1980)

	Age group (years)	1964–67	1968–71	1972–75	1976–80
Total no. of patients	<35	17	17	18	28
treated	35–54	251	210	161	137
	55–74	191	181	171	206
Cumulative percentage	<35	70·6	58·8	65·8	60·7
surviving by age group	35–54	54·6	56·6	60·7	59·6
	55–74	53·2	46·2	56·7	53·8
χ^2 for trend (1 d.f.) (controlling for stage)		0·11	3·63	0·11	0·09
P<		0·80	0·10	0·80	0·80

Table 4. Percentage surviving 2 years by age group and date of treatment (1964–1984)

	Age group (years)	1964–67	1968–71	1972–75	1976–80	1981–84
Total no. of patients treated	<45	105	85	65	87	90
	45–74	354	323	285	284	248
Cumulative percentage surviving by age group	<45	74·3	77·5	76·1	66·4	67·7
	45–74	69·5	63·5	69·8	70·9	69·2
χ^2 (1 d.f.) (controlling for stage)		0·04	0·63	0·05	3·57	2·73
$P<$		0·90	0·50	0·90	0·10	0·10
Death rate ratio*		1·045	0·822	0·938	1·500	1·433

*Ratio of observed to expected deaths in period (controlling for stage) in the <45 age group, divided by the same ratio for those aged 45–74

Table 5. Percentage surviving 2 years by age group and date of treatment (1964–1984)

	Age group (years)	1964–67	1968–71	1972–75	1976–80	1981–84
Total no of patients treated	<35	17	17	18	28	35
	35–54	251	210	161	137	127
	55–74	191	181	171	206	176
Cumulative percentage surviving by age group	<35	88·2	64·7	77·8	67·9	65·6
	35–54	68·5	72·2	72·0	71·1	67·3
	55–74	71·8	59·8	69·3	69·3	70·6
χ^2 for trend (1 d f.) (controlling for stage)		1·19	3·82	0·02	0·94	2·41
$P<$		0·30	0·10	0·90	0·50	0·20

Table 6. Carcinoma of cervix 1964–1984: tumour differentiation by age group and date of treatment (percentage of total cases referred in each age group and time period)

Degree of differentiation	Age group (years)	1964–67	1968–71	1972–75	1976–80	1981–84
Good	<45	3·8	15·3	15·4	16·1	13·3
	45–74	7·9	13·6	16·8	21·5	10·5
Moderate	<45	7·6	25·9	44·6	26·4	27·8
	45–74	9·0	27·9	46·0	31·0	37·1
Poor	<45	12·4	22·4	24·6	47·1	51·1
	45–74	18·9	22·3	25·6	34·5	44·4
Not known	<45	76·2	36·5	15·4	10·3	7·8
	45–74	64 1	36·2	11·6	13·0	8·1

no major changes in population in our catchment area during this period and we are unaware of any change in gynaecological referral pattern. Most patients in the West of Scotland were treated by radical radiotherapy. All patients were staged by FIGO criteria, and all patients assigned to the same FIGO stage were treated by exactly the same radiotherapeutic technique, irrespective of age or histology. Patients were allocated to the appropriate stage after an examination under anaesthesia, cystoscopy, proctoscopy, chest radiograph and intravenous

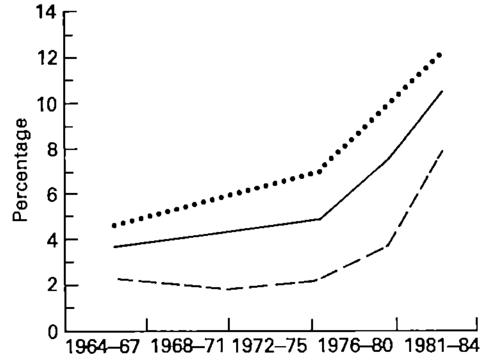

Fig. 1. Carcinoma of cervix 1964–1984. Percentage of total cases aged <35 years by date of treatment . . . , Stages I & II; ———, all stages; – – –, stages III & IV

urogram. Other investigations such as abdominal ultrasound or isotope scanning of liver or bone were performed if indicated and available at that time. Virtually all the women with Stage I had invasive tumour (Stage IB). The very small number of patients with micro-invasive disease (Stage IA) were for the most part evenly distributed between age groups and over time.

Early lesions (Stages I and II) received two intracavity insertions 1 week apart using 'Manchester'-type applicators, containing radium (1964–1974) or radio-caesium (1975–1984). The total dose to point 'A' was 60 Gy at a dose rate of 0·55 Gy/h. This was followed by 3 weeks (14 fractions) treatment with 4 MeV X-rays to parallel opposed diamond-shaped fields with the radium or caesium covered by a specially shaped wedge. This gave a combined dose to point 'A' of 76·5 Gy and a pelvic side-wall dose of 49·5 Gy. More advanced lesions (Stages III and IV) were treated over 4 weeks with 4 MeV irradiation to the whole true pelvis using a four-field box technique. A dose of 42·5 Gy was given in 20 fractions followed by a single intracavity insertion giving point 'A' a further 33·5 Gy

Forty-three patients were treated by radical hysterectomy or other major surgery before radiotherapy. These patients were treated by 4 weeks (42·5 Gy) X-ray treatment then a vaginal caesium insertion. Sixteen of these patients had histologically proven regional lymph node involvement but for the purposes of survival analysis the original pre-operative clinical staging has been used.

Between 1980 and 1984, 135 patients receiving intracavity radiation as part of radical radiotherapy were treated by Selectron after-loading machine, 268 by conventional caesium sources and 22 by both methods. When the Selectron patients were compared with patients conventionally treated during the same period, the tumour-free survival with a 2-year follow-up was similar (73 and 68% respectively). The use of the Selectron after-loading machine did not significantly alter prognosis after controlling for age and stage distribution.

We divided patients into three age bands: under 35, 35–54 and 55–74 years. Patients aged 75 and over were not included in the study. As the number of patients aged under 35 was small, patients in Stages I and II and in Stages III and IV were grouped together. In order to provide sufficiently large samples to detect any difference between FIGO Stages I and II, a further analysis was performed, with the patients being divided into two age groups: under 45 years and 45–74 years. All but 15 of the 1588 patients treated up to and including 1980 were followed up for at least 5 years. To detect any recent trends in survival, a comparison was also made on the basis of 2 years' survival data. This included patients treated up to the end of 1984. Only five patients out of 1926 were lost to follow-up within 2 years of treatment. Table 1 shows the distribution of patients by age and stage between 1964 and 1984. Survival analysis used the log rank method (Peto *et al.* 1977) and associated χ^2-tests of statistical significance. Further tests for trend in survival with age and time period of treatment were made using the Cox proportional hazards model (Cox 1972).

Results

The number of patients aged under 35 referred to the Western Infirmary, Glasgow, with invasive carcinoma of cervix doubled during the last 10 years of this study (Fig. 1, Table 4). There is

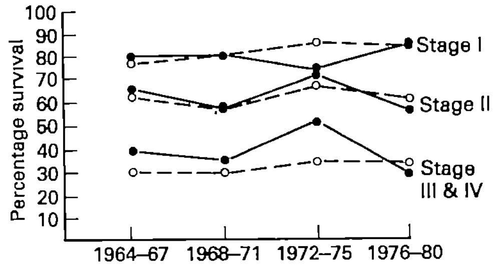

Fig. 2. Carcinoma of cervix 5-year survival by age and stage. ●——●, <45 years; O– – –O, 45–74 years

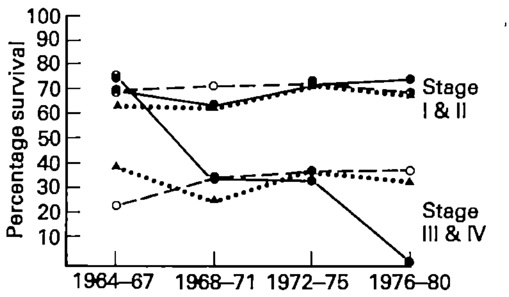

Fig. 3. Carcinoma of cervix 5-year survival by stage and age. ●——●, <35 years; ○- - -○, 35–54 years; ▲· · · ·▲, 54–74 years.

no clear evidence that younger patients (aged either <35 or <45) have a worse prognosis than those in older age groups (Tables 2–5). Although there has been some trend among younger patients towards poorer survival in the short term, despite the greater frequency of Stage I disease in the younger age groups (Table 1), even after survival analysis is controlled for stage distribution neither of the observed differences in survival experience after 1976 is statistically significant at the 5% level (Table 4). There is very little difference indeed in 5-year survival between age groups, and those aged <35 or <45 appear to fare no worse than older patients.

There has been little change, stage for stage, over the last 20 years in the survival experience of patients in the West of Scotland treated by the same radiotherapy technique (Figs 2–5). The only subgroup which shows a trend towards a worse prognosis over time consists of patients <35 who presented with Stage III or IV disease. Fortunately, the number of patients in this category is extremely small (averaging five in each of the time periods analysed). The apparently excellent survival of patients <35 who presented with advanced disease between 1964 and 1967, for example, is based on only one death among four patients. Where there are more patients available for analysis, such as when the younger age group is expanded to include all patients <45, there is no significant change in the prognosis for patients presenting with advanced disease.

Application of the Cox proportional hazards model to analysis of trends in survival experience (using the five age groups <35, 35–44, 45–54, 55–64 and 65–74, and controlling for all four FIGO stages) did show a statistically significant relation ($P<0{\cdot}05$) between young age and poorer survival over 2 years for those treated between 1981 and 1984.

No significantly adverse effect associated with young age could be discerned at any of the other time periods studied, either over 2 or 5 years. There was very little relation between survival, either in the short or the long term, and time period of treatment for any age group, including those aged <35 and 35–44. Over the study period as a whole, neither age at diagnosis nor time period of treatment were significant prognostic factors independent of stage.

During the study period there has been little change in the proportion of patients presenting with squamous tumour, adenocarcinoma or the rarer forms of carcinoma of cervix, either between age groups or over time.

Since 1975 there has been a marked increase in the number of tumours graded as poorly differentiated, especially amongst patients aged <45 (Table 6). This variable had a statistically significant effect upon 2-year survival independent of age and stage for the period 1976–1980, but not for 1981–1984. No trends in differentiation can be discerned before 1972 as most of the tumours were then given no pathological grade.

Discussion

The number of women <35 years referred has more than doubled in the 21-year period of the study and reflects accurately the overall trend in Scotland. The number of women with invasive cancer of cervix aged 25–34 notified to cancer registries increased by a factor of 2·3 between 1960 and 1980 (Cook & Draper 1984). Although the incidence is rising in younger women, they are more likely to have early stage tumours. In all five time-bands of this study, almost twice as many women <45 presented with Stage I tumour (almost all Stage IB) compared with older women. In the last time period (1981–

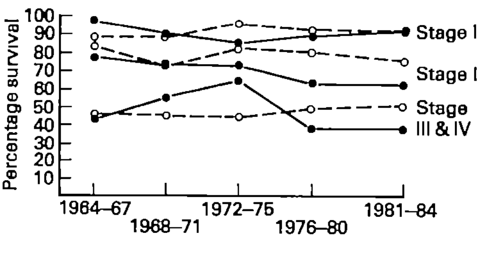

Fig. 4. Carcinoma of cervix 2-year survival by age and stage. ●——●, <45 years; ○- - -○, 45–74 years.

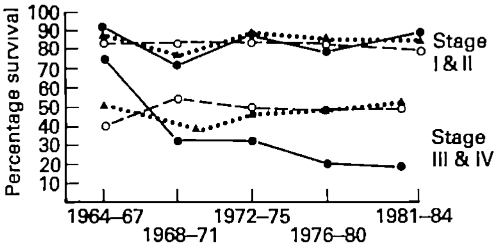

Fig. 5. Carcinoma of cervix 2-year survival by age and stage ●——●, <35 years; ○- - -○, 35–54 years; ▲· · · ·▲, 54–74 years.

1984) 48% of those aged <45 had Stage I disease. We cannot explain the increased frequency of earlier presentation in younger women. Perhaps screening in the West of Scotland is more effective in these age groups. This suggestion is supported by data from Grampian and Tayside which are recognized as the best screened regions of Scotland (Duguid *et al.* 1985; MacGregor & Teper 1978). In Grampian region, where screening encompassed many women aged >40, mortality at all ages fell by 36% between 1968 and 1976 compared with a reduction of only 9% in the rest of Scotland. In Tayside, where the initially screened population contained more younger women than in Grampian, mortality fell by 39% between 1968 and 1976 amongst women aged 35–54 years. Screening outside Tayside and Grampian has been less intensive and has had little overall effect on mortality but the reduction in death rate amongst women aged 35–54 over this period was similar throughout Scotland (Grampian 22·5%, Tayside 39%, the remainder 29%) suggesting screening of younger women is equally effective and has had some effect on mortality. More recent data from Tayside show that this reduction continued through to 1981 (Duguid *et al.* 1985).

Although there has been a marked rise in the number of poorly differentiated tumours, especially amongst younger women, the overall effect upon survival is far from clear. Numerous attempts have been made in the past to correlate histopathological appearances with outcome after radiotherapy. Whilst some found prognostically significant differences (Reagan *et al.* 1957; Wentz & Reagan 1959), no difference could be found by others (Gunderson *et al.* 1974; Jakobsen *et al.* 1985). In a small series of patients <35 years anaplastic histology was held to be an important prognostic factor; seven of nine patients died (Hall & Monaghan 1983).

Age had no adverse effect on prognosis in two other British series of patients treated by radiotherapy (Russell *et al.* 1987; Ashby & Smales 1987). Younger patients treated at the Christie Hospital in Manchester between 1971 and 1978 were more likely to present with early tumours and had a better overall survival. Stage-for-stage survival was better for younger patients and this is statistically significant for Stage IB cases (Russell *et al.* 1987).

Treatment methods seem to be unimportant. In a large German co-operative study, survival was identical for patients aged under or over 35 years treated by Wertheim's hysterectomy (Baltzer *et al.* 1982). However, the effect of age upon prognosis remains controversial and other investigators have reported poorer prognosis for younger patients (Stanhope *et al.* 1980; Yeoh & Spittle 1986; Mendenhall *et al.* 1984).

Our data suggest that the increased mortality in younger patients in the West of Scotland is due to an increase in the number of younger women with disease rather than to a more virulent form of the disease. As it has been suggested that the increased incidence seen in women born around 1951 and later is likely to increase through their life expectancy (Draper & Cook 1983) continued monitoring of the outcome of treatment in this group seems to be essential, particularly in view of our results for the period 1981–1984.

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Intraperitoneal radioimmunotherapy for ovarian cancer

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Summary. Twenty-eight patients with assessable residual ovarian cancer after cytoreductive surgery and chemotherapy received intraperitoneal I-131 labelled monoclonal antibodies. There was no response in eight patients with tumour nodules >2 cm, a partial response in two of the 15 patients with tumour nodules <2 cm, and a complete response in three of the other five patients with positive peritoneal washings. A further six patients received Y-90 labelled monoclonal antibodies for residual ovarian cancer. There was no response in one patient with nodules >2 cm, and a partial response in one of the other five patients with tumour nodules <2 cm. The non-specific radiation dose in the peritoneal cavity from the infused isotope was measured by lithium fluoride thermoluminescent dosimetry (TLD). The radiation dose received by the peritoneal serosa was <500 cGy and was not sufficient to account for the observed tumour response. Significant bone marrow suppression was observed with I-131 activities greater than 120 mCi and with Y-90 activities greater than 13 mCi. The haemopoietic bone marrow is the dose-limiting organ in patients receiving radioimmunotherapy.

Ovarian cancer is now the cause of more deaths than any other gynaecological malignancy in the Western World (DHSS 1987; Silverberg & Luberg 1987; Becker *et al.* 1984). Most patients present with diffuse intraperitoneal spread and require extensive debulking surgery and postoperative chemotherapy. There have been considerable advances in both methods of treatment, with many patients having small volume disease after surgery (Hacker *et al.* 1983; Piver & Baker 1986). There is an additional response rate of 40–70% after postoperative chemotherapy (Neijt *et al.* 1984; Wiltshaw *et al.* 1986). Unfortunately most of these patients relapse locally, so that the overall prognosis remains as poor as it was 50 years ago (Silverberg & Luberg 1987).

One reason for the poor prognosis is the failure to consolidate the initial response after surgery and chemotherapy. External beam radiotherapy can eradicate small volume disease in many sites, but radiation doses of 4500–5000 cGy are required. These radiation doses are not tolerated by the whole peritoneal cavity, as renal and hepatic radiation tolerance are exceeded at 2000 and 3000 cGy respectively (Dembo 1987). Low-dose (3000 cGy in 20 fractions) whole abdominal radiotherapy has been reported to control residual disease after surgery alone (Martinez *et al.* 1985; Dembo 1985), although others have found little benefit after combined surgery and chemotherapy (Hainsworth *et al.*

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1983; Blackledge *et al.* 1987). Intraperitoneal radiocolloids (phosphorous-32, yttrium-90) can deliver doses of several 1000 cGy to the peritoneal serosa. The radiation dose diminishes rapidly with depth, only 1% of the surface serosal dose penetrating as far as 2 mm (Currie *et al.* 1981). Radiocolloids are therefore likely to be effective in eradicating only residual disease <2 mm in diameter. Combining radiocolloids with external beam irradiation has been found to be toxic (Klassen *et al.* 1985).

The development of monoclonal antibodies to tumour-associated antigens has raised the possibility of using radiolabelled antibodies to target tumoricidal radiation doses to tumour cells (Liechner *et al.* 1981; DeNardo *et al.* 1985; Hammersmith Oncology Group and Imperial Cancer Research Fund 1984). There have been numerous reports of successful gamma camera imaging with I-123 and In-111 labelled antibodies given intravenously (Ballon *et al.* 1979; Bersche *et al.* 1982; Mach *et al.* 1981). Biopsy data in patients have shown preferential binding of radiolabelled antibody, with tumour to normal tissue ratios of 3:1–5:1. However, less than 0·01% of the injected radiation activity is targeted to each gram of tumour (Epenetos *et al.* 1986*b*), and tumoricidal radiation doses are unlikely.

Residual recurrent disease in ovarian cancer is often confined to the peritoneal cavity, and intraperitoneal rather than intravenous administration of radiolabelled antibodies may be more appropriate. A distinct advantage in using the intraperitoneal route has been reported both in animals (Rowlinson *et al.* 1987) and man (Colcher *et al.* 1987). Tumoricidal quantities of I-131 labelled antibody have been detected on tumour cells in malignant ascites (Ward *et al.* 1987). We have found that some malignant effusions have been controlled by intracavitary radiolabelled antibodies (Pectasides *et al.* 1986). The importance of antibody specificity is suggested by the observation that recurrence can occur from antigen negative cells rather than the previously positive cells (Epenetos *et al.* 1986*a*). It is not known whether microscopic solid residual disease, or small macroscopic disease will also respond to intraperitoneal radioimmunotherapy. We have recently completed a phase I/II study of intraperitoneal I-131 labelled monoclonal antibodies in ovarian cancer. A second phase I/II trial using Y-90 labelled monoclonal antibodies has recently been started. The preliminary results from both studies will be discussed.

Patients and methods

From September 1983 until October 1987, 36 patients with ovarian cancer received intraperitoneal I-131 labelled monoclonal antibodies. Selected patients were thought to have residual tumour after cytoreductive surgery and chemotherapy. Response data were obtained from 28 patients with assessable disease. The remaining eight patients received adjuvant treatment or were not assessed after treatment and are only included for pharmacokinetic and toxicity data. Two patients were referred without receiving previous chemotherapy; one had only undergone surgery, and the other had received postoperative pelvic radiotherapy. The remainder had received postoperative chemotherapy with platinum-containing regimens. Two patients also received postoperative whole abdominal radiotherapy.

Between March and December 1987, 18 patients received Y-90 labelled monoclonal antibodies intraperitoneally after surgery and postoperative chemotherapy. Only six of these patients had assessable residual disease.

All patients had epithelial ovarian carcinoma, and were accepted for the study if their original tumour demonstrated positive staining (>50% tumour cells) with one or more of the panel of available monoclonal antibodies (see below). Pretreatment assessment was by laparoscopy, unless disease was detectable clinically or radiologically. The mean age of patients treated was 56·1 years (range 31–75), and the time between primary surgery and radioimmunotherapy ranged from 6 weeks (pre-operative chemotherapy) to 5 years (mean 14 months).

Three patients presented originally with stage IV disease, three with stage II, one with stage Ic, and one with stage Ia: the remainder presented with stage III disease. Those with assessable disease were divided into three groups depending on the volume of residual tumour before radioimmunotherapy.

Both studies were approved by the Hammersmith Hospital ethics committee and informed consent was obtained from all patients.

Assessment and response criteria

Patients were assessed clinically and radiologically at first, and if there was no evidence of residual disease, by laparoscopy before receiving treatment. Laparoscopy was performed 8 to 12 weeks after treatment if there was no clinical evidence of relapse. Response to therapy was classified as: complete response (CR) defined by complete disappearance of all tumour at laparoscopy, and partial response (PR) defined by a 50% reduction in tumour size. Patients who did not have a post-treatment laparoscopy were said to have 'no evidence of disease' (NED) if clinically disease free.

Radiolabelled antibodies

Patients were selected for radioimmunotherapy if their original tumour histology demonstrated positive immunocytochemical staining with one or more of the following four monoclonal antibodies: HMFG1, HMFG2, AUA1 and H17E2, which have all been shown to bind to adenocarcinoma-associated antigens expressed by most epithelial ovarian tumours (Epenetos *et al.* 1982; Arklie *et al.* 1981; Travers & Bodmer 1984).

Iodine-131 emits beta particles and gamma rays with a half-life of 8 days. The former account for more than 90% of the absorbed dose, but have an average tissue penetration of only 2 mm. Antibodies were iodinated by a modification of the iodogen method described previously (Fracker & Speck 1978; Epenetos *et al.* 1987). Yttrium-90 is a pure beta emitter with a half-life of 64 h. These beta particles have a greater energy and can penetrate up to 11 mm in tissue. Yttrium-90 was conjugated to the antibody using a DTPA chelate (Hnatowich *et al.* 1985).

Treatment protocol

The treatment procedure has been described previously (Epenetos *et al.* 1987). Patients receiving I-131 labelled antibodies were given potassium iodide for 2 days before and 28 days after treatment to suppress I-131 uptake by the thyroid. An intraperitoneal catheter (usually a peritoneal dialysis catheter) was inserted under local or general anaesthesia (at laparoscopy). Patients who had catheters inserted 'blind' under local anaesthesia received 1 mCi of Tc-99m colloid instilled with 500 ml saline. Gamma camera images confirmed catheter position and uniform intraperitoneal isotope distribution. The radiolabelled antibody was infused with 1500 ml of 0·9% saline over 30 min. Patients were nursed in a radiation-controlled environment for 5 days until their total body I-131 content was <30 mCi before being discharged from hospital.

Pharmacokinetics and dosimetry

Since January 1987 all patients have had 12-hourly estimations of blood radiation activity, and a continuous 5-day urine collection to estimate renal isotope excretion. Blood radiation activity and renal excretion are expressed 'decay corrected' (assuming that radioactive decay does not occur).

The bone marrow is irradiated by beta particles in the marrow circulation and adjacent bone. The radiation dose to the bone marrow is estimated, assuming that the haemopoietic bone marrow constitutes 2·2% of the body weight (International Commission on Radiological Protection No. 23 1975) or 25% of the blood volume. This dose is calculated according to the MIRD formulation:

$$\text{Marrow radiation dose in cGy} = 0{\cdot}25\, A \times S$$

where A is the integrated whole blood radiation activity in mCi-h and S is the S factor for haemopoietic marrow being both the radiation source and the target organ (Snyder *et al.* 1978). Radiation to the marrow from bone is difficult to quantify, and for non-bone seeking elements such as iodine, was considered negligible. Bone marrow suppression was classified as:

+, WBC 3–3·9 × 10^6/l and/or platelets 75–99 × 10^9/l.
++, WBC 2–2·9 × 10^6/l and/or platelets 50–75 × 10^9/l
+++, WBC 1–1·9 × 10^6/l and/or platelets 25–49 × 10^9/l.
++++, WBC <0·9 × 10^6/l and/or platelets <25 × 10^9/l.

We have also measured the radiation dose in the peritoneal cavity by lithium fluoride thermoluminescent dosimetry (TDL). The dosimeter comprised 30–40 lithium fluoride rods (6· × 1 mm), heat-sealed in a plastic catheter and inserted into the peritoneal cavity during the pretreatment laparoscopy. The TLD catheter remained in the peritoneal cavity for 5 days, by which time 90% of the isotope had decayed. The lithium fluoride absorbs the same quantity of radiation energy as the surrounding normal tissue, but stores a proportion of this energy in its crystal lattice. After removal of the TLD catheter the rods were heated in an oven to 300°C. The stored energy is liberated as light (thermoluminescence), the quantity of light being proportional to the radiation dose. The TLD catheters were calibrated against standard solutions containing known activities of I-131 and Y-90 (Fig. 1). TLD catheters only measure the non-specific dose to the serosal surface. They cannot measure the radiation dose targeted to tumour cells.

Results

Tumour responses

Iodine-131 labelled antibodies. The 28 assessable patients were divided into three groups depending on the volume of disease before therapy (Table 1). There was no response in eight patients with tumour nodules >2 cm. Two of the 15 patients with nodules <2 cm had a partial response at laparoscopy. No nodules were seen in either patient, although both had positive peritoneal cytology. Since then, both these patients have relapsed clinically. Three of the five patients with positive cytology were found to have negative washings at laparoscopy after treatment. Two of these patients have relapsed intra-abdominally at 14 and 30 months.

Yttrium-90 labelled antibodies. One patient had bulky disease with tumour nodules >2 cm and ascites requiring paracentesis at fortnightly intervals. She died of local progressive disease 8 weeks after treatment, but with no recurrence of her ascites Five patients had small tumour nodules before treatment. One patient who had extensive small tumour nodules was found to have had a partial response, with only two nodules visible at post-treatment laparoscopy. This patient was treated again, this time with I-131 labelled monoclonal antibodies and is now in complete remission. The other four patients failed to respond.

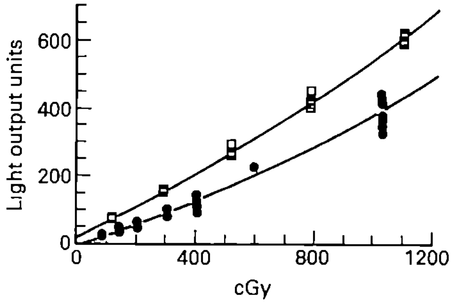

Fig. 1. Calibration curves for lithium fluoride TLD rods in solutions of yttrium-90 (□) and iodine-131 (●).

Pharmacokinetics and dosimetry

Patients without ascites had 26% of the injected dose of I-131 labelled monoclonal antibodies in their blood by 40 h (Fig. 2). Following this peak, the labelled antibody was cleared mono-exponentially from the circulation with a mean clearance half-life of 50 h. Patients receiving Y-90 labelled antibodies had similar kinetics, although the clearance half-life is only 30 h (due to the shorter physical half-life). Different pharmacokinetics were seen in two patients who received I-131 labelled antibodies for malignant ascites. Only a maximum of 6% of the injected dose was found in their blood, with peak radiation activities occurring 100 h after injection. The radiation dose to bone marrow from the blood radiation activity (calculated by the MIRD formulation), and the radiation dose to the peritoneum (measured by TLD), are shown in Table 2.

Toxicity

Toxicity from intraperitoneal radioimmunotherapy can be categorized as complications from catheter insertion and fluid administration, immunological complications, and radiation complications. There were two serious complications associated with catheter insertion, one patient developed a subphrenic abscess, and another required a laparotomy for bowel perforation. There were several complications following the administration of antibody. Five patients reported mild to moderate abdominal pain and eight patients complained of nausea or vomiting. There were no classical type I or type III hypersensitivity reactions, although several patients developed a mild pyrexia lasting less than 72 h, and two patients complained of a 'flu-like' illness.

The most serious toxicity was due to irradiation of bone marrow (Table 2). Patients who received more than 120 mCi of I-131 developed neutropenia or thrombocytopenia 3–5 weeks

Table 1. Tumour response to Y-90 and I-131 labelled monoclonal antibodies by size of tumour nodules

Size of tumour nodules	No. of patients	Radioisotope	No. of responses
>2 cm	8	I-131	0
	1	Y-90	0
<2 cm	15	I-131	2 (partial)
	5	Y-90	1 (partial)
Microscopic	5	I-131	3 (complete)

after treatment. Bone marrow suppression in patients receiving I-131 labelled antibody was directly correlated with the estimated bone marrow dose. Mild bone marrow suppression (+) was observed with estimated bone marrow doses of 143 cGy, and severe toxicity (++++) at 281 cGy. The nadir of the blood counts occurred 30–40 days after treatment.

Patients receiving Y-90 labelled antibodies also developed bone marrow suppression 30–40 days after treatment. This occurred with Y-90 activities greater than 6 mCi, associated with estimated marrow radiation doses of only 16 cGy (Table 2). Bone marrow suppression was reversible in all patients. Two patients receiving I-131 labelled antibodies and one patient receiving Y-90 labelled antibodies required platelet transfusions. No patient died as a result of neutropenia or thrombocytopenia, although one patient died of progressive tumour during a period of marrow suppression.

Discussion

In this study we have examined the toxicity and efficacy of I-131 and Y-90 labelled monoclonal antibodies in patients with persistent ovarian cancer after surgery and chemotherapy. Responses were confined to patients with small tumour nodules or positive cytology. It is now known that radiolabelled antibodies do not penetrate far into tumour spheroids (Sutherland *et al.* 1987), and the lack of efficacy in patients with large nodules is not surprising. It is difficult to assess a response by laparoscopy, as nodules seen before treatment may be missed subsequently. Two patients with small tumour deposits and three patients with positive cytology appear to have responded to treatment with I-131 labelled antibodies. Unfortunately, all but one of these patients has relapsed, the remaining patient being disease free 40 months after treatment.

Yttrium-90 was chosen to replace I-131 as the radiolabel because of its pure beta radiation of high energy (Order *et al.* 1986). Beta particles have a range limited to a few millimetres, and unlike gamma rays are absorbed locally. The beta particles from I-131 have a mean range of 2 mm in tissue, and cannot penetrate far into tumour if concentrated on the surface. Yttrium-90, however, has a maximum range of 11 mm in tissue, and could penetrate into the centre of macroscopic deposits. Even so, if the antibody is concentrated on the tumour surface, the radiation dose at 2 mm will be a small fraction of the surface dose. We have not treated enough patients with Y-90 labelled antibodies to determine a response rate. So far one of the five patients with macroscopic disease has responded, and is disease free 12 months after treatment.

Radiocolloids such as colloidal gold-198 (100 mCi) or colloidal phosphorous-32 (15 mCi) give a radiation dose to the serosal surface of 5000 cGy or more (Currie *et al.* 1981). The dose to the serosal surface from radiolabelled antibodies is less than 1000 cGy due to systemic absorption. This radiation dose is not sufficient to account for the tumour responses observed, and it is proposed that antibody specificity increases the radiation dose to tumour cells. Systemic absorption of the antibody is probably via lymphatics, which accounts for the low blood radiation activities in patients with malignant ascites (Fig. 2). In this situation the radiolabelled antibody

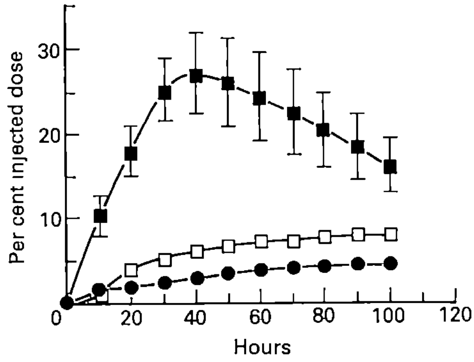

Fig. 2. Blood radiation activity (decay-corrected) following I-131 labelled monoclonal antibodies in patients with and without ascites The error bars represent ± 2 SEM values. ■, Mean of nine 'dry' patients; □, ●, two ascites patients.

Table 2. Bone marrow suppression and radiation dose to haemopoietic marrow and peritoneal serosa in patients receiving I-131 or Y-90 labelled monoclonal antibodies

Radiolabel	Patient no.	Radioactivity (mCi)	Mean peritoneal dose (cGy)	Bone marrow dose (cGy)	Toxicity
I-131					
	1	130	339	177	++
	2	158	423	281	++++
	3	120	501	200	+++
	4	146	431	200	++
	5	105	290	143	+
Y-90					
	6	17	385	45	+++
	7	17·6	273	45	+++
	8	15	347	37	++
	9	6	152	16	+
	10	15	249	20	++
	11	15	283	33	++
	12	13	443	32	++
	13	15	215	31	++
	14	12·5	346	20	+
	15	16·3	309	23	+

may remain in the peritoneal cavity (like a colloid), with a high non-specific radiation dose. Isotopes with long physical half-lives (iodine-131, 8 days) should be used with caution in patients with ascites. Yttrium has a physical half-life of only 64 h and would be safer in this situation.

Absorption of radiolabelled antibody exposes the rest of the body to beta radiation. This radiation dose is decreased if there is lymphatic obstruction (as in ascites), or if isotopes with short decay half-lives are used. The haemopoietic bone marrow is extremely vascular and is irradiated by its circulating blood. We have estimated the radiation dose to marrow to be 143 cGy in a patient receiving 105 mCi I-131 (associated with mild toxicity), and 281 cGy in a patient receiving 158 mCi I-131 (associated with serious toxicity). The 50% lethal dose to marrow (LD_{50}) in man without bone marrow transplantation is thought to be 300–450 cGy (Hall 1978). The calculated radiation dose to bone marrow from Y-90 labelled antibodies is only 16 cGy for 6 mCi and 45 cGy for 17 mCi. The latter dose was associated with significant bone marrow suppression. Our marrow radiation dose calculation assumed that the only radiation source was the blood in the bone marrow. This does not appear to be true for Y-90 labelled antibodies. Unbound yttrium is a bone-seeking metal, and marrow irradiation from Y-90 in adjacent bone may be important.

From our initial studies it would appear tumour response is confined to patients with either microscopic or tiny macroscopic residual disease. Y-90 may be a better isotope, due to its greater beta particle energy and shorter half-life. However, if bone absorption is an important factor, these advantages may be outweighed by increased bone marrow toxicity. It may be possible to combine radioimmunotherapy with external beam irradiation, as the radiation dose to the peritoneal serosa is low with the former. The combination would increase the radiation dose in tumour nodules without the toxicity found with combined radiocolloids and external beam radiation (Klassen *et al.* 1985). Bone marrow suppression would, however, still remain a significant factor.

Intraperitoneal radioimmunotherapy remains an experimental treatment. The development of monoclonal antibodies with greater tumour affinity and specificity, more appropriate isotopes, or humanized antibodies (that do not provoke an immune response), can be expected to make some impact in the future.

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North Staffordshire/Wigan assisted delivery trial

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Summary. In a trial conducted at the North Staffordshire and Billinge Maternity Hospitals (NSMH and BMH) a total of 264 women who required an assisted delivery in the second stage of labour were randomly assigned to be delivered either by Kobayashi silicone cup ventouse or by forceps. A larger proportion (90%) of those assigned to the forceps group were actually delivered by the allocated instrument compared to those in the silicone cup group (73%). However, there was a significantly higher rate of maternal morbidity in terms of perineal trauma and discomfort in the forceps group. No differences in neonatal morbidity were detected.

Both in Europe, where the vacuum extractor remains the most popular instrument for performing an operative vaginal delivery, and in the English-speaking countries, where forceps are the preferred instrument, debate continues with respect to the relative merits of each. As over 50 000 operative vaginal deliveries are done each year in Britain this remains an important area for research where any difference in morbidity will affect large numbers of women and babies. There have only been three randomly controlled prospective trials comparing the two instruments (Lasbrey *et al.* 1964; Vacca *et al.* 1983; Fall *et al.* 1986). In all three trials the ventouse was associated with statistically significantly fewer maternal complications. The babies born by ventouse had an increased frequency of cephalhaematoma in all three trials and of mild neonatal jaundice in the Vacca trial. Other forms of scalp injury were more common in babies born by forceps.

The reason most often cited by English-speaking obstetricians for not using the ventouse is the possible occurrence of increased neonatal morbidity. In an attempt to improve the neonatal outcome in ventouse deliveries, a pliable silicone rubber cup ('Silc-cup': Menox, Gothenberg) has been introduced. This instrument does not have a rigid edge and moulds to the shape of the baby's head, not requiring a chignon to be formed in the same way as a metal cup. A clinical assessment of this instrument showed it to be satisfactory (Maryniak & Frank 1983) and subsequently two small studies have compared the silicone rubber cup with forceps.

From a randomized study, Dell *et al.* (1985) concluded that both forceps and the silicone rubber cup were effective instruments for assisted vaginal delivery. Berkus *et al.* (1985) found that the silicone rubber cup caused less maternal trauma than forceps and was not associated with any increase in fetal morbidity. That study included only women delivered successfully with a silicone rubber cup and matched with the next sequential woman delivered with forceps on the labour ward.

We report here a two-centre randomized study using the silicone rubber cup alone in comparison with forceps, as the first-line manage-

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ment. The aims of the study were to delineate the role of the silicone rubber cup as well as to measure any maternal and neonatal effects in comparison with forceps, the established mode of assisted delivery. The principal measures of maternal morbidity were maternal perineal trauma, postpartum haemorrhage and maternal discomfort at delivery. The measures of fetal morbidity were scalp and facial skin trauma, cephalhaematoma, retinal haemorrhage, jaundice and acidosis at birth.

Subjects and methods

The trial was conducted at the North Staffordshire and Billinge Maternity Hospitals which have annual delivery rates of over 6000 and nearly 4000 respectively. The assisted delivery rate at both hospitals is 8–9% and the caesarean section rate 10–12%. Both methods of assisted vaginal delivery were in use at the hospitals before the start of the trial. Patients eligible for inclusion in the study were those with singleton pregnancies, a cephalic presentation and a gestation of at least 35 completed weeks. The trial protocol, which was approved by the ethics committees and consultants of both hospitals, included a provision for not entering a woman into the study if the doctor felt that a particular instrument was especially indicated for the assisted delivery.

The method of randomization was by a consecutive series of sealed, opaque envelopes prepared at the National Perinatal Epidemiology Unit. There was 1:1 randomization within balanced blocks of varying size (4–10).

Regardless of the ultimate mode of delivery, the women remained in the group to which they were originally allocated for the purposes of analysis.

Between September 1987 and February 1988 there were 390 assisted instrumental deliveries at the two hospitals of which 264 were included in the trial. Of the 126 deliveries not entered into the study a proportion were not eligible, for example multiple or preterm deliveries. In the group not entered there were 23 ventouse deliveries (a number performed where the cervix was not fully dilated) and 103 forceps deliveries. Twenty of this group were delivered by consultants and 10 were delivered under general anaesthesia; the remainder were not entered into the study because of 'severe fetal distress' or 'operator preference'. There is no reason to believe that they were importantly different from those entered into the study: in particular there is no evidence that potentially more difficult deliveries were not included in the trial as the operative failure rates in the non-participants were low (ventouse 8%, forceps 2%).

The trial was designed to include 300 patients, which was the number we estimated would be available within the time limits of the study. With this sample size the power of the trial to detect a decrease in maternal morbidity, in terms of third-degree tears, from 20% to 10%, as reported by Vacca *et al.* (1983) was 72%. The power of the study in detecting the difference in neonatal jaundice reported by Vacca *et al.* (1983) (20% in the forceps group compared with 30% in the ventouse group) was 68%.

Once a decision had been made to perform an assisted vaginal delivery the midwife helping the operator was asked to record the position, station and the amount of caput and moulding as found by the doctor, before opening the envelope. The time of opening the envelope was recorded. The forceps used were either Neville–Barnes or Kiellands. The silicone rubber cup was used with negative pressure gradients being provided by an Egnell Universal Suction Pump (Egnell-Ameda Ltd, Taunton), taking the pressure directly to 0·6–0·8 bar. Progress had to be made with traction, and two detachments were allowed. A successful delivery was defined as the ability to deliver the woman with the randomly assigned method.

In the analysis of the results, failures in the group delivered with the silicone rubber cup (silc-cup group) were defined as 'partial' or 'true': a 'true' failure was one in which there was no descent with traction or where repeated cup application had been required; a 'partial' failure was one in which there was rotation or descent to the perineum, or both, with only one application of the cup and where the delivery was either normal or by low-cavity forceps. In the forceps group a 'true' failure was one in which the blades had been successfully applied but where no descent occurred; the remainder were classified as 'failed application' of the blades, usually because analgesia was considered insufficient.

Details of each procedure including the extent of maternal trauma were recorded by the operator immediately after delivery. The neonatal senior house officer noted information about the infant's condition at birth and again at the

Table 1. Characteristics of patients in the two study groups

Descriptive variables	Silicone cup (n=132)	Forceps (n=132)
Age (years)	25 (4)	25 (5)
Nulliparity	95 (72%)	96 (73%)
Gestational age (weeks)	39·9 (1·3)	40·1 (1·4)
Birthweight (kg)	3·46 (0·498)	3·44 (0·445)
Fetal scalp electrodes	95 (72%)	99 (75%)
Fetal blood sampling	29 (22%)	33 (25%)
Scalp pH	7·3 (0·07)	7·3 (0·09)
Abnormal CTG	66 (50%)	77 (58%)
Meconium in labour	20 (15%)	24 (18%)
Indication for delivery		
Delay in second stage	47 (36%)	48 (36%)
Fetal distress	47 (36%)	58 (44%)
Delay and distress	28 (21%)	18 (14%)
Shorter second stage	10 (7%)	8 (6%)
Length of labour (min)		
First stage	506 (247)	519 (274)
Second stage	79 (55)	71 (50)
Oxytocin	71 (54%)	84 (64%)
Position of head		
Occipito-anterior	82 (62%)	96 (73%)

Results are means (SD) or n (%) values as appropriate.

postnatal examination. At the North Staffordshire Maternity Hospital (NSMH) Minolta recorded levels of jaundice were obtained (Jaundice-meter 101/Narco Scientific Air Shields Division). At the Billinge Maternity Hospital (BMH) jaundice was assessed by serum bilirubin levels. At the NSMH any abnormalities of the babies were noted by one of us (N.L.) and at BMH by the paediatric senior house officer with referral to the consultant. In an unselected cohort of 30 infants, fundoscopy was performed by N.L., using cyclopentolate hydrochloride BP 0·5% w/v eye-drops for mydriasis. The babies wore caps during the fundoscopy to mask the method of delivery. It was not possible for the other outcomes to be assessed 'blind'.

The woman was examined before discharge by both the ward sister and the senior house officer at the NSMH and by J.P. or one staff midwife at the BMH. Details of perineal bruising, post-delivery pyrexia and use of analgesia were noted. All the women were formally questioned about the delivery and puerperium by the family planning sister at the NSMH and by one staff midwife and J.P. at the BMH. A full analysis of these questionnaires will be the subject of a future report.

Statistical methods

For frequency variables we used the χ^2-test of homogeneity between the two methods: Fisher's exact probability test was also used in 2 × 2 contingency tables. For continuous variables Student's t-test was used, and since the sample size was large the differences between proportions were tested using normal tables. The 95% confidence intervals are quoted for differences in proportion and for odds ratios (Breslow & Day 1980) where appropriate.

Results

The characteristics of the participants, their labours as well as indications for delivery, were comparable in the two groups (Table 1). There were somewhat more deliveries for fetal distress and more occipito-anterior positions in the forceps group. The actual mode of delivery and operator status is shown in Table 2.

In 12 women the allocated method was not attempted. In four this was because spontaneous vaginal deliveries had occurred. Six of the remainder were allocated to the silc-cup group but in three the equipment was not working or sterilized, in one there was 'severe fetal distress',

Table 2. Actual mode of delivery in the two study groups and operator status

	Allocated group	
Mode of delivery	Silicone cup (n=132) n (%)	Forceps (n=132) n (%)
Silicone cup	97 (73)	10 (8)
Forceps	28 (21)	119 (90)
Spontaneous vaginal	5 (4)	2 (1)
Caesarean section	2 (2)	1 (1)
Operator status		
Senior house officer	60 (45)	65 (48)
Registrar	69 (52)	63 (48)
Senior registrar	1 (1)	1 (1)
Consultant	0 (0)	1 (1)
Midwife (normal delivery)	2 (2)	2 (2)

in another a 'vaginal band' and in the last a fetal blood sample had been taken followed by persistent bleeding. In two women allocated to the forceps group the silicone rubber cup was used because on re-examination the cervix was found to be only 9 cm dilated. In none of the women allocated to the silc-cup group was the cervix recorded as not fully dilated.

The mean pressure used in the application of the silicone rubber cup was 0·7 (SD 1) bar. The mean time of application to first pull was 2 min 30 s (SD 1 min 20 s) and the mean time from application to delivery was 5 min 30 s (SD 1 min 20 s). In 30 deliveries one pull was used, in 60 two pulls, in 25 three pulls, in five four pulls, and in 12 the number of pulls was not recorded. In 89 deliveries the cup was applied once only, in 34 it was applied twice, and in nine deliveries three times.

Although the average time from opening the envelope to delivery (17 min, SD 10 min) was the same in both groups, in the subgroup of women where the indication for instrumental delivery was fetal distress, the time in the silc-cup group (13 min) was shorter than that in the forceps group (16 min). This difference was statistically significant ($P<0{\cdot}05$) with a 95% CI for the difference of 0·6 to 4·3 min. Analgesia required for delivery is detailed in Table 3. Women in the silc-cup group were less likely to have a pudendal nerve block ($P<0{\cdot}001$, odds ratio 0·34, 95% CI 0·21 to 0·57) and more likely simply to have perineal infiltration for delivery ($P<0{\cdot}001$, odds ratio 5·30, 95% CI 2·50 to 11·11).

Success of delivery

Overall, 97 (73%) patients in the silc-cup group and 119 (90%) patients in the forceps group were delivered by the allocated instruments (Table 2). All the records of the failures of delivery were carefully analysed (Table 4). In

Table 3. Analgesia for delivery in the two study groups

Analgesia	Silicone cup (n=132) n (%)	Forceps (n=132) n (%)	Odds ratio	(95% CI)
Epidural	47 (35)	44 (33)	1·11	(0·67 to 1·85)
Pudendal and perineal	42 (32)	76 (58)*	0·34	(0·21 to 0·57)
Perineal	40 (30)	10 (8)**	5·36	(2·50 to 11·11)
None	1 (1)	1 (1)		
General anaesthesia	2 (2)	1 (1)		

* $P<0{\cdot}001$ observed difference 26% (95% CI 14% to 38%)

** $P<0{\cdot}001$ observed difference 22% (95% CI 13% to 31%)

Table 4. Reasons for failure in the two study groups

Group	Position of head (n)	Actual mode of delivery (n)
Silicone cup (n=35)		
True failure (n=15)	Occipito-anterior (8)	Neville–Barnes (8)
	Occipito-posterior (7)	Kielland's (4)
		Neville–Barnes (2)
		Caesarean section (1)
Partial failure (n=12)	Occipito-anterior (6)	Normal delivery (2)
		Neville–Barnes (4)
	Occipito-posterior (6)	Normal delivery (1)
		Neville–Barnes (5)
Method not attempted (n=8)		Spontaneous vaginal (2)
		Neville–Barnes forceps (5)
		Bird posterior metal cup (1)
Method attempted outside protocol (cervix 9 cm dilated)		Caesarean section (1)
Forceps (n=13)		
True failure (n=1)	Occipito-posterior	Caesarean section (1)
Failed application (n=8)	Occipito-posterior	Silicone cup (8)
Method not attempted (n=4)		Spotaneous vaginal (2)
Cervix not fully dilated		Silicone cup (2)

the silc-cup group there were 15 true failures, 12 were women who failed to progress in labour and only three required assisted delivery for fetal distress. This is reflected in the finding that the time spent pushing in this group of 15 women was 60 min compared with the overall mean of 35 min; the babies were bigger in the failure group, with a mean birthweight of 3·67 kg compared with the overall mean of 3·45 kg, and examination before randomization showed that they had a greater amount of caput.

Maternal trauma

The description of perineal and vaginal damage was made at the time of repair (Table 5). Women were more likely to have perineal and vaginal trauma in the forceps group: 12% in the forceps group and 5% in the silc-cup group had third-degree tears; 2% in the silc-cup group and 8% in the forceps group had vaginal tears extending to the fornices. When questioned, a larger number of women in the forceps group complained of

Table 5. Perineal and vaginal trauma

Trauma	Silicone cup (n=132) n (%)	Forceps (n=132) n (%)
Perineum*		
Intact	8 (6)	6 (5)
First-degree tear	11 (8)	2 (2)
Second-degree tear/cut	107 (81)	108 (82)
Third-degree		
Sphincter	6 (5)	13 (10)
Anal mucosa	0 (0)	3 (2)
Vagina**		
No extension	97 (73)	76 (58)
Small extension	6 (5)	14 (10)
Extension to fornix	2 (2)	10 (8)
Not recorded	27 (20)	32 (24)

* $P<0{\cdot}05$ χ^2 11·07 d.f.3.

** $P<0{\cdot}005$ χ^2 11·15 d.f.2.

moderate to severe discomfort during the delivery, but this difference was not statistically significant. Table 6 shows the results of the questionnaire administered on the day before discharge, when significantly less discomfort was reported in the silc-cup group (odds ratio 0·50, 95% CI 0·28 to 0·89).

The estimated mean blood loss in the forceps group was significantly larger than that in the silc-cup group (375 ml, SD 200, compared with 315 ml, SD 150, 95% CI for the difference 11 to 107 ml). However, the drop in haemoglobin (between the last reading before delivery and 3 days after delivery), 1·2 g/dl, was the same in both groups, as was the packed cell volume on day 3, 32·99%. The total number of patient days of pyrexia (>37·5° C) was similar in both groups (20 days) as was the average number of paracetamol tablets taken (10).

Neonatal morbidity

The condition of the babies immediately after birth was very similar in the two groups. Two babies in the silc-cup group were transferred to the neonatal unit. One died from multiple congenital abnormalities, the other recovered without complication from meconium aspiration.

Minolta recordings or serum bilirubin levels were available for 80% (210) of the babies. Arbitrary levels of >15 Minolta units and >200 μg/l were chosen to define jaundice. In assessing rates of jaundice, it is worth noting that the groups were comparable in respect of use of oxytocin (40%) and breast-feeding (50%). There was no significant difference in the rates of jaundice between the silc-cup group (13·1%) and the forceps group (15·3%) (95% CI for difference 11·7% to 7·3%), thus ruling out the hypothesized increase in jaundice of 10%.

Neonatal trauma is summarized in Table 7.

Table 6. Perineal discomfort on day 4

Perineal discomfort	Silicone cup (n=132)	Forceps (n=132)
No discomfort	9 (7)	3 (2)
Slight discomfort	37 (28)	26 (20)
Moderate discomfort	46 (35)	52 (39)
Severe discomfort	9 (7)	18 (14)
Not questioned	31 (23)	33 (25)

$P<0{\cdot}05$ χ^2 8·27 d f.3.

There were more babies with bruising in the silc-cup group than in the forceps group (odds ratio of scalp or facial bruising was 1·63, 95% CI 0·97 to 2·73), but more serious trauma was more common in the forceps group. One of the two facial nerve palsies in the forceps group was transient; and Erb's palsy in another baby was associated with shoulder dystocia.

Of the 30 babies who had fundoscopy two babies (one in each group) had a single small (non-macular) retinal haemorrhage. One baby born in the silc-cup group had a subconjunctival haemorrhage.

There was no relation between fetal blood sampling or the use of a scalp electrode (Copeland's or single-helix spiral) and the development of jaundice in the silc-cup group. Nor was there a relation between the use of scalp electrode or blood sampling in labour and the presence or absence of scalp bruising. Indeed, in 14 of the 22 babies in the silc-cup group in whom fetal blood was sampled, no bruising was noted at all.

However, in those 41 babies in the silc-cup group in whom bruising was measured the size of the bruise was 50% larger in those who had fetal blood sampling (7·43 cm, SD 3·6 compared with 5·13 cm, SD 2·22) ($P<0{\cdot}05$, 95% CI for the difference in size 0·36 cm to 4·22 cm).

Discussion

The aim of the trial was to compare the performance of the silicone rubber cup with the more commonly used method of operative vaginal delivery, forceps, in normal clinical practice. The main disadvantage of the silicone rubber cup was the increased rate of failure of delivery. This has been found in previous studies (Dell *et al.* 1985; Hammarstrom *et al.* 1986).

Although the position of the occiput is thought to be a predictor of failure (Hammarstrom *et al.* 1986), we had 31 completely successful rotations and deliveries with the silicone rubber cup. In a further five women there was rotation and descent to the perineum, the delivery being completed by 'low-cavity' forceps. Success of delivery was not related to parity and was more likely when assisted delivery was for fetal distress than when it was for failure to progress. Whatever the position, in patients with fetal distress the silicone rubber cup was quicker than forceps, thus confirming the findings of Vacca *et al.* (1983). Our explana-

Table 7. Neonatal morbidity

	Silicone cup (*n*=132)	Forceps (*n*=132)
Scalp/facial bruising *n* (%)	50 (38)	36 (27)
Cephalhaematomata	2	2
Facial cuts	0	2
Facial nerve palsy	0	2
Erb's palsy	0	1
Low Apgar scores		
<3 at 1 min	2	4
<7 at 5 min	2	2
Meconium only at delivery *n* (%)	12 (9)	15 (7)
Umbilical artery sampling *n* (%)	99 (75)	83 (63)
pH Mean (SD)	7·26 (0·9)	7·25 (0·8)
Number with cord pH		
<7·2	20	21
<7·1	4	1
Jaundiced* *n* (%)	13/99 (13·3)	17/111 (15·32)
Minolta units (NSMH) Mean (SD)	12·6 (3)	12·4 (3)
Bilirubin (BMH) (μmol/1) Mean (SD)	101 (72)	107 (72)
Phototherapy *n* (%)	4 (3)	5 (4)
Fundoscopy	15	15
Small retinal haemorrhage	1	1
Subconjunctinal haemorrhage	1	0

* >15 Minolta units or >200 μmol/l bilirubin.

tion for this finding is the lesser requirement for operative analgesia with the silicone rubber cup and the relative ease with which it may be applied. The finding that in up to eight women the operator was unable to perform a Kielland's rotation because of inadequate analgesia, but was able to perform a ventouse extraction substantiates the impression that a ventouse delivery is less painful for the woman. Previous adequately controlled studies have reported less maternal trauma with the ventouse (Dell *et al.* 1985; Greis *et al.* 1981; Lasbrey *et al.* 1964; Vacca *et al.* 1983). In the present study we have provided further evidence to support this finding; there is now no doubt that a policy of using vacuum extraction rather than forceps is associated with an important reduction in maternal trauma.

In the assessment of neonatal morbidity no increase in jaundice was found in the silc-cup group, and the expected increase in scalp bruising was balanced by facial injuries in the forceps group. Apart from the cephalhaematomata in each group there was no serious scalp trauma; in particular there was no infection or necrosis. Trauma was no greater in the silc-cup group even if the cup became detached.

Roberts & Stone (1978) reported a fetal haemorrhage after fetal blood sampling and a ventouse delivery. We found no relation between scalp electrode use or blood sampling and the occurrence of bruising. However, we did find that if bruising occurred, the size of the bruise was likely to be larger if blood sampling had been performed.

Our results and experience have demonstrated that the silicone rubber cup compares favourably with forceps in terms of maternal discomfort and trauma. Neonatal trauma was no greater in the silc-cup group. The silicone cup was not as effective an instrument in achieving a delivery as forceps; this was particularly so with prolonged pushing, increased caput, and a large baby. This failing has also been demonstrated in a randomized controlled trial comparing the silicone rubber cup with the metal cup (Cohn *et al.* 1989). We feel that there is an important place for the silicone rubber cup on the delivery suite. It is simple to orientate, easy to apply and unlikely to cause any harm even if it becomes detached. A logical policy would be to use the cup for most low-cavity deliveries and well-flexed rotational deliveries, especially in fetal distress. On the basis of the findings reported by

Vacca *et al.* (1983) where the silicone rubber cup is likely to fail it may be better to use the metal cup rather than forceps. A trial is at present underway at the North Staffordshire Maternity Hospital which is designed to assess a policy of vacuum extraction using a metal or silicone rubber cup compared with forceps.

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A multicentre randomized trial comparing delivery with a silicone rubber cup and rigid metal vacuum extractor cups

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Summary. A total of 258 women requiring assisted delivery where vacuum extraction was thought to be suitable were randomly allocated to delivery with a new silicone rubber cup or metal vacuum extractor cups. There was a tendency for the silicone rubber cup to effect delivery more quickly and to cause less scalp trauma, but to fail to effect delivery on more occasions than metal cups. However, none of these differences was statistically significant. There were no statistically significant differences in the rates of birth canal trauma, maternal blood loss, or neonatal jaundice. The silicone rubber cup produced a cosmetically more acceptable chignon than the metal cups. The introduction of vacuum extractors with silicone rubber cups into obstetric units should be encouraged.

Two prospective randomized trials comparing the vacuum extractor with the obstetric forceps, where the staff have been equally well trained in both methods, have been reported (Lasbrey *et al.* 1964; Vacca *et al.* 1983). Both showed that the vacuum extractor was slightly less effective in completing delivery but had significant advantages in reducing maternal trauma and analgesic requirements.

Despite these favourable reports and its widespread acceptance in continental Europe and elsewhere, the vacuum extractor has remained unpopular in the UK and North America. The self-perpetuating tradition for using obstetric forceps has been reinforced by some adverse reports of fetal scalp trauma and cranial injuries associated with the vacuum extractor (Ahuja *et al.* 1969; Agüero & Alvarez 1962; Huntingford 1961). In a review of the literature Plauché (1979) suggested that these were the exception rather than the rule and could be reduced with careful use of the vacuum extractor.

In an attempt to reduce severe scalp trauma and also minimize the cosmetically unsightly caput succedaneum, Kobayashi introduced a silicone rubber cup which was 65 mm in diameter and had a stainless steel valve. A recent modification of the Kobayashi cup is the Silc-cup which is entirely fashioned from silicone rubber and has no valve (Fig. 1). These cups move away

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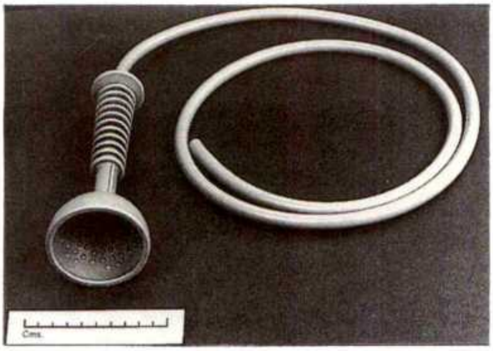

Fig. 1. The silicone rubber cup (the Silc-cup).

from the principle of developing a pediculate caput, relying instead on a larger surface area to develop sufficient traction. Maryniak & Frank (1984) have reported their extensive experience with the Kobayashi cup and noted a remarkably low rate of major fetal scalp trauma. Berkus *et al.* (1985, 1986) compared this cup with forceps and normal delivery in a non-randomized cohort study. They reported less maternal trauma and no evidence of increased fetal trauma in the silicone rubber cup group compared with the forceps group. They also commented that in those cases where the silicone rubber cup failed to complete delivery there was no increase in maternal or fetal morbidity. Dell *et al.* (1985) compared a plastic and a silicone rubber cup with low-cavity forceps in a randomized trial. They recorded less maternal soft tissue and fetal scalp trauma with both vacuum groups, but the cephalhaematoma rate was higher than in the forceps group. Hastie & MacLean (1986) reported a retrospective analysis of a silicone rubber cup and Kiellands forcep deliveries and noted a greater success rate with the forceps in malrotation. Hammarström *et al.* (1986) conducted the only randomized study comparing the Kobayashi with the Malmström cup. They showed that the silicone rubber cup effected delivery more promptly and caused fewer scalp injuries, but it failed to effect vaginal delivery on more occasions than the Malmström cups.

We have conducted a much larger randomized study to assess the relative merits and disadvantages of the silicone rubber and traditional metal vacuum cups.

Patients and methods

Doctors trained in the use of the vacuum extractor recruited participants from the Northern General Hospital in Sheffield, the Rotherham District General Hospital, the Leicester General Hospital and the North Staffordshire Maternity Hospital in Stoke-on-Trent. Patients eligible for entry into the trial were all those with a singleton pregnancy and cephalic presentation and where instrumental assistance was required for delivery. As soon as the decision had been made that a woman and her baby were suitable for vacuum extraction, a random treatment allocation was made by opening a sealed envelope. Randomization was computer generated in blocks of 20, allocated to each participating centre in 60s.

The comparison was of 'an intention to deliver by silicone rubber cup' with 'an intention to deliver by metal cup'. All outcomes are reported irrespective of the final method of delivery.

A full range of metal cups was used (40 to 60 mm, Malmström, anterior and posterior Bird and 'New Generation' cups) depending on availability and operator preferences. The cups were attached to an electric vacuum pump. Negative pressure did not exceed 500 mmHg. Details of each procedure, including the extent of maternal trauma and estimated blood loss, were recorded by the operator immediately after delivery. All timings were taken from when the cup was applied.

Failure to deliver the woman with three 'pulls' (one 'pull' being traction during a single maternal contraction) or two or more cup detachments was recorded as a 'method success outside protocol' if the intended cup was eventually successful or as a 'method failure' if an alternative method was used.

The infant was assessed immediately after birth by a paediatrician and again 48 h later when a careful inspection of the scalp was made. Scalp markings were divided into three categories: 'none'; 'minor' (bruising ≤5 cm diameter or minor abrasions); or 'major' (bruising >5 cm diameter or cephalhaematoma). At this assessment the paediatrician was 'blind' to the randomization.

With 300 subjects the trial would have a power of 80% of demonstrating at the 5% level a 50% increase in failed delivery or a 50% decrease in the frequency of neonatal scalp trauma and jaundice with the silicone rubber cup. The χ^2 (with Yates' correction where applicable) and Student's *t*- statistical tests were used in analysis. Odds ratios and 95% confidence intervals are shown where applicable.

Table 1. Characteristics of patients in two study groups

Descriptive variable	Silicone rubber cup (n=131)	Metal cup (n=127)
Town of delivery		
Sheffield	38	37
Rotherham	27	27
Stoke-on-Trent	34	34
Leicester	32	29
Maternal and fetal		
Maternal age (years) Mean (SD)	25·5 (4·4)	26·1 (5·6)
Nulliparous	106 (81%)	96 (76%)
Gestation >37 weeks	124 (95%)	121 (96%)
Incomplete cervical dilatation	18 (13%)	8 (6%)
Spontaneous onset of labour	103 (79%)	98 (77%)
Oxytocin in second stage	85 (65%)	87 (68%)
Epidural in second stage	69 (52%)	68 (54%)
Deflexed head	99 (76%)	101 (84%)
Occiput posterior or transverse	45 (34%)	44 (35%)
Moulding ++ or +++	27 (21%)	28 (22%)
Large caput	18 (14%)	25 (20%)
Indication for operative delivery		
Delay second stage	66 (50%)	63 (50%)
Fetal distress	46 (35%)	50 (39%)
To shorten second stage	19 (15%)	14 (11%)
Operator status		
Consultant/senior registrar	18 (14%)	13 (10%)
Registrar	89 (68%)	78 (62%)
Senior house officer	24 (18%)	36 (28%)
Neonatal		
Birthweight (kg) Mean (SD)	3·44 (0·51)	3·51 (0·50)
Head circumference (cm) Mean (SD)	35·5 (1·4)	35·6 (1·4)
Male sex	69 (53%)	79 (62%)

No statistically significant difference in any variable.

By the end of the study period 265 patients had been recruited. Seven had to be excluded for a variety of reasons (multiple gestation, randomization error and lost data). The remaining 258 patients are reported here.

Results

Of the 258 participants in the trial, 131 were allocated to the silicone rubber cup and 127 to the metal cup. The comparability of the two groups is presented in Table 1. There were more patients with an incompletely dilated cervix in the silicone rubber cup group and this group tended to be delivered by more senior obstetricians. There were similar numbers of infants in the occiput posterior position and with higher degrees of moulding. The infants in the silicone rubber cup group tended to have less caput. There was no difference in the indication for operative delivery.

The eventual method of delivery after randomization is shown in Table 2. There were no statistically significant differences between the two types of cup. Only one patient in each group started with the presenting part above the ischial spines, and both these ended up as method failures. Some operators originally found the silicone rubber cup difficult to apply because of its larger size, especially when the head was low on the perineum. However, with experience they overcame this problem sometimes by performing an episiotomy first.

Traction could be applied sooner with the silicone rubber cup (the first pull coming within 3 min in 46·6% compared to 40·5%). This was reflected in the numbers delivered within 6 min (29·5% in the silicone rubber cup group compared with 23·3% for the metal cup group). The

Table 2. Outcome once randomization has taken place

Mode of delivery	Silicone rubber cup (*n*=131)	Metal cup (*n*=127)
Spontaneous vaginal	4 (3·1%)	7 (5·5%)
Method success (≤3 pulls or <2 detachments)	97 (74·0%)	99 (78·0%)
Method success outside protocol (>3 pulls or ≥2 detachments)	9 (6·9%)	8 (6·3%)
Delivered with intended cup	106 (80·9%)	107 (84·3%)
Method failure	21 (16·0%)	13 (10·2%)

No significant differences between the two groups for 'method success' P=0·3 and 'method failure' P=0·26.

fact that a few patients in the silicone rubber cup group had an episiotomy cut first did not appear to bias this finding. The modal number of pulls to achieve delivery was two for both cups in the 'method success' group. There was no difference in the number of patients requiring more than two pulls (P=0·95). Delivery was effected with no cup detachments in 80% of the silicone rubber cup deliveries and 92% of the metal cup deliveries. However, there was no significant difference in the number of patients requiring more than one reapplication of the cup (P=0·25).

Patients in the 'method failure' groups are more fully described in Table 3 and compared with patients in whom the method succeeded. Both cups failed more frequently when a more difficult delivery could be anticipated—cervix not fully dilated, deflexed head, occiput posterior, with a high degree of moulding and a large amount of caput.

There were no differences in the amount of perineal and vaginal trauma (Table 4). Ten patients in the silicone rubber cup group and six in the metal cup group were estimated to have a blood loss of 500 ml or more.

One infant was stillborn in the silicone rubber group despite the electronic heart trace being recorded as normal up to the point of delivery. Paediatric assessment revealed that the infant had died several hours earlier and the fetal heart trace must have been an artefact. There were no neonatal deaths. Although there was a tendency for there to be less scalp trauma in the silicone rubber cup group than the metal cup group, the differences were not statistically significant (Table 5). Neither were there any differences in the frequency or severity of neonatal jaundice in the two groups (Table 5). There were no significant differences in the 1- and 5-min Apgar scores, the mean umbilical vein pH, the numbers of infants requiring intubation at birth or the numbers requiring admission to SCBU between the two groups (Table 6).

Discussion

This was a 'management' trial designed on similar lines to the Portsmouth operative delivery trial (Vacca *et al.* 1983) to compare a silicone rubber cup with conventional metal vacuum extractor cups for operative delivery in the second stage of labour in normal clinical practice. By making it a multicentre study in a mixture of teaching and district general hospitals we were able to recruit a large number of patients quickly and increase the generalizability of the results. The groups were well randomized and had very similar characteristics. The silicone rubber cup group included babies that were slightly smaller and had less caput, but this was probably balanced by a small excess of primigravidae and patients whose cervix was incompletely dilated.

The silicone rubber cup completed delivery somewhat less often (81% against 84%); however, this was not a statistically significant difference. The success rate with the metal cups (84%) was very similar to that reported in the prospective trials by Vacca *et al.* (1983), 87·5%, and Lasbrey *et al.* (1964), 90%. As would be expected, both cups failed more often with more difficult deliveries.

The ease and speed of application of the silicone cup was commented on by Hammarström *et al.* (1986). It is superior to the metal cup as it comes as one piece and so there is no need to assemble it and also traction can be started immediately rather than waiting for a chignon to develop. This could be of use in cases of fetal distress in the second stage of labour.

The silicone rubber cup detaches from the scalp more frequently but this is not associated with a higher neonatal morbidity. As long as

Table 3. Characteristics of the 'method fail' group compared to the 'method success' group

Characteristic	Silicone rubber cup		Metal cup	
	Fail (*n*=21)	Success (*n*=97)	Fail (*n*=13)	Success (*n*=99)
Maternal and fetal				
Nulliparous	19 (90%)	76 (78%)	10 (77%)	76 (78%)
Incomplete cervical dilatation	6 (29%)	11 (11%)	3 (23%)	5 (5%)
Occiput posterior or transverse	11 (52%)	28 (29%)	5 (38%)	34 (34%)
Deflexed head	7 (33%)	20 (21%)	2 (15%)	19 (19%)
Moulding ++ or +++	7 (33%)	18 (19%)	4 (31%)	19 (19%)
Large caput	3 (14%)	14 (14%)	1 (8%)	19 (19%)
Indication for operative delivery				
Delay in second stage	14 (67%)	49 (51%)	5 (38%)	53 (53%)
Distress	6 (29%)	33 (34%)	6 (46%)	36 (36%)
To shorten second stage	1 (5%)	15 (15%)	2 (15%)	10 (10%)
Neonatal				
Birthweight (kg) Mean (SD)	3·64 (0·39)	3·32 (0·51)	3·62 (0·39)	3·54 (0·50)
Head circumference (cm) Mean (SD)	35·9 (1·59)	34·9 (1·17)	36·6 (1·53)	35·2 (1·33)
Reason for failure				
Cephalopelvic disproportion	6 (29%)		6 (46%)	
Insufficient traction	10 (48%)		6 (46%)	
Difficult application	3 (14%)		0 (0%)	
Others	2 (9%)		1 (8%)	
Eventual delivery method				
Direct forceps	12		8	
Rotational forceps	2		1	
Lower-segment caesarean section	4		3	
Metal cup	3		—	
Silicone rubber cup	—		1	

No statistically significant differences in any variable.

progress is being made it is probably safe to apply the silicone rubber cup more than twice. Operators commented on the rather gentle separation at cup detachment compared with the tendency of metal cups to 'fly off'.

There was no difference in birth canal trauma between the two groups, although it is remarkable how few extensions of the episiotomy followed delivery. Entrapment of the vaginal epithelium leading to laceration is less likely with the soft edge of the silicone rubber cup.

Classifying neonatal scalp trauma is very difficult unless one observer sees all the infants, which is not possible in a multicentre trial. The Portsmouth delivery trial had a rate of 14·1% for neonatal scalp trauma in the vacuum group sug-

Table 4. Maternal trauma sustained in the two study groups

Extent of trauma	Silicone rubber cup (*n*=131)	Metal cup (*n*=127)	Significance (*P*)	Odds ratio	95% CI
None	8 (6%)	6 (5%)	0·95	1·31	0·44 to 3·90
First-degree tear	18 (14%)	14 (11%)	0·90	1·29	0·61 to 2·71
Episiotomy only	97 (74%)	94 (74%)	0·95	1·00	0·57 to 1·77
Extension into					
Anal sphincter	1 (1%)	1 (1%)	0·95	0·97	0·06 to 15·6
Upper vagina	3 (2%)	4 (3%)	0·95	0·72	0·16 to 3·29
Others	0 (0%)	1 (1%)	0·95	—	

Table 5. Neonatal scalp trauma (as assessed at 48 h) and neonatal jaundice in the two study groups

Extent of trauma	Silicone rubber cup (*n*=131)	Metal cup (*n*=127)	Significance (*P*)	Odds ratio	95% CI
None	58 (44%)	45 (36%)	0·5	1·45	0·88 to 2·38
Minor	36 (27%)	42 (33%)	0·75	0·77	0·45 to 1·31
Major	18 (14%)	23 (18%)	0·75	0·72	0·36 to 1·39
(cephalhaematoma)	8 (6%)	7 (5%)	0·9	1·11	0·39 to 3·16
Unavailable for 48 h assessment	19 (15%)	17 (13%)			
Jaundice					
All	17 (13·0%)	16 (12·6%)	0·975	1·03	0·50 to 2·14
No therapy	16 (12·2%)	12 (9·4%)	0·9	1·33	0·60 to 2·95
Phototherapy	1 (0·8%)	4 (3·2%)	0·25	0·24	0·07 to 5·82

Table 6. Other neonatal morbidity

Neonatal morbidity	Silicone rubber cup (*n*=131)	Metal cup (*n*=127)	Significance (*P*)	Odds ratio	95% CI
Apgar score <7 at 1 min	28 (21%)	20 (15%)	<0·75	1·45	0·77 to 2·72
Apgar score <7 at 5 min	4 (3%)	1 (1%)	<0·5	3·97	0·44 to 35·9
Endotracheal intubation	7 (5%)	11 (9%)	<0·75	0·60	0·22 to 1·63
Admission to SCBU	3 (3%)	4 (3%)	<0·95	0·72	0·16 to 3·29
Umbilical pH Mean (SD)	7·22 (0·13)	7·21 (0·13)			
(No. infants tested)	(45)	(50)			

gesting that a number of the 'minor' lesions in our study would have been reported as 'normal' in Portsmouth. More abrasions might have been expected with the metal cup but this was not the case. Our results do still suggest that the silicone rubber cup tends to cause less scalp trauma than the metal cup. Hammarström *et al* (1986) also found this tendency, and Dell *et al.* (1985) were impressed with the more 'natural'-looking caput following delivery with silicone rubber cups.

Several authors have commented that cephalhaematomata are overdiagnosed in infants who have been born by vacuum extraction and that the soft bruised lesion which is not sharply delineated by the scalp sutures and tends to run a more benign course would be better called a 'subcutaneous ecchymoses' (Plauché 1979) or an 'extensive scalp effusion' (Chalmers 1965). The cephalhaematoma rate in this study was just under 6%, which is the same as the average calculated by Plauché (1979) on reviewing reports on 8000 vacuum extractions. Berkus *et al.* (1986) and Hastie & MacLean (1986) both comment that if the silicone rubber cup fails to complete delivery and thus delivery with forceps or caesarean section is required, the neonatal morbidity is not increased. Because this has not been found to be the case with metal cups in the past, they went on to suggest that trial of silicone rubber vacuum extractor is safe and might avoid a difficult mid-pelvis forceps delivery or caesarean section.

There was no difference in the neonatal jaundice rates, the figure of 13% being considerably lower than rates of 25–35% quoted in some series for vacuum extraction. However, unless all infants undergo serum bilirubin estimation the assessment of jaundice is very subjective.

In summary, the results of our trial confirm those reported by Hammarström *et al.* (1986): although there is a tendency for the silicone rubber cup to fail to effect delivery more often than metal cups, the four out of five cases in which it is successful are delivered more promptly and with somewhat less scalp trauma. The introduction of this cup into obstetric units should be encouraged.

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Audit of medical response to antenatal booking history

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Summary. A retrospective review of 600 obstetric case-notes, covering the years 1978 to 1984, was performed independently by two assessors. The medical response to 22 risk factors, recorded at booking by the midwife, was assessed. The medical staff recognized 69% of the risk factors recorded at booking and responded appropriately to 82% of these. The standard of care improved over the period studied. The accuracy of our conclusions was greatly enhanced by carrying out each assessment in duplicate with arbitration by a third assessor when necessary, and it is proposed that all audits of medical practice should themselves be audited in this way.

Antenatal care embodies both the management of problems which arise during pregnancy and screening for factors that warrant further action. The most important point of contact for the detection of these factors is the first antenatal attendance (booking visit), where the history provides the most useful source of information. Inadequate care can result from failure to identify risk factors. Techniques such as history-taking by computer have been suggested to improve the true recording of the antenatal history (Lilford & Chard 1981). Only one previous audit has examined the doctor's response to recorded information and this showed inadequacies in medical performance (Chng *et al.* 1980).

We have assessed the quality of this facet of antenatal care at St James's University Hospital in Leeds over the last 10 years. Our audit, unlike the only previous study to address this issue, was conducted by two independent medical assessors. As a significant difference in the conclusions recorded by the initial assessors was found, a further assessor arbitrated on each point of disagreement.

Materials and methods

A retrospective review of 600 obstetric notes was performed encompassing the first 150 women delivered in 1978, 1980, 1982 and 1984. In this Health Authority, St James's is the only hospital with obstetric wards; all antenatal bookings are done here and subsequent care is usually shared with the general practitioner.

Every woman is seen by a midwife, who takes a detailed obstetric history and carries out the basic observations: blood pressure, urinalysis and weight. A doctor of senior registrar grade, or above, then reviews the history, examines the patient, requests the appropriate investigations and plans the subsequent follow-up. In the present study, the medical response at booking was reviewed for 22 factors selected on the basis that each requires a specific response by the booking doctor. These factors and the recommended medical action or response are listed in Table 1. The risk factors were further graded into categories 1–3 according to our perception of how serious omissions would be in medical practice. Those in category 1 (factors 1–9 in Table 1) are considered so important that failure of recognition or action should be deemed a failure of antenatal care. Those in category 2 (factors 10–16 in Table 1) were judged to be of sufficient

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Table 1. Selected risk factors recorded in 600 obstetric case-notes; recommended action and proportion recognized by the booking doctors (1978–1984)

Factor	Recommended action or response	Factors recorded *n*	Factors recognized *n* (%)
Category 1			
1 Maternal age >37	Offer amniocentesis	14	9 (71)
2 Neural-tube defect in previous pregnancy	Offer amniocentesis/ultrasound/ alpha-fetoprotein	5	5 (100)
3 Previous baby >4500 g	Glucose tolerance test	2	2 (100)
4 Mediterranean ethnic origin	Blood test for thalassaemia	6	2 (33)
5 Pakistani/Indian ethnic origin	Blood test for thalassaemia	42	20 (48)
6 Patient on specific drug therapy	Ascertain the management	10	7 (70)
7 Rubella non-immune	Offer vaccination after delivery	29	28 (97)
8 Rh-negative mother	Anti-D globulin injections	80	80 (100)
9 Sickle disease	Monitor fetal growth, check serial urine specimens, avoid hypoxia/ dehydration in labour	—	—
Category 2			
10 Previous baby with birthweight <5th centile	Consider ultrasound growth check, biophysical monitoring, fetal movement chart	18	3 (17)
11 Previous unexplained antepartum stillbirth	Glucose tolerance test	1	1 (100)
12 Chronic renal disease and hypertension	Check serial BP, urinalysis, uric acid and creatinine	—	—
13 Recurrent cystitis	Serial midstream specimens of urine	15	5 (33)
14 Prevention of DVT/prosthetic heart valve	Consider heparin/cover labour with antibiotics	13	10 (77)
15 West African/Caribbean in origin	Sickle cell test	13	13 (100)
16 Previous caesarean section	Consider method of delivery	29	27 (93)
Category 3			
17 Chronic hypertension/pregnancy-induced hypertension	Check serial BP, urinalysis, uric acid and creatinine	52	18 (35)
18 TB contact	Chest X-ray	3	3 (100)
19 Previous pre-eclampsia/eclampsia	Check serial BP, USS, urinalysis, uric acid and creatinine	9	2 (22)
20 Previous retained placenta or primary postpartum haemorrhage	Obstetrician present at delivery	21	11 (52)
21 Previous preterm labour	Consider diagnosis of incompetent cervix with need for cerclage	6	5 (83)
22 Mid-trimester abortion in preceding pregnancies	Consider diagnosis of incompetent cervix with need for cerclage	8	6 (75)
23 Three or more terminations of pregnancy	Consider diagnosis of incompetent cervix with need for cerclage	—	—
24 Third-degree tear	Obstetrician at delivery	3	3 (100)

Some factors are linked to more than one recommended action If any of these recommended actions was followed, credit was given for action taken importance that failure of recognition or action should be considered a shortfall in antenatal care, and those in category 3 (17–24) were considered either less important or more controversial.

The clinician was considered to have noted a condition if it was mentioned specifically in the case-notes or commented upon in the booking letter to the general practitioner or if it resulted in an appropriate response or management plan. The medical responses in Table 1 represent our assessment of optimal medical care according to the 'state of the art' over the last 10 years. Some of the appropriate responses are specific, such as the requirement to offer prenatal diagnosis to women over the age of 37, or glucose tolerance testing where a previous baby weighed >4·5 kg. For other risk factors, however, care was judged adequate provided some action was taken, the particular form of management being left to individual clinical discretion. Thus, for a woman with a history of caesarean section we would expect to see that the doctor had made some attempt at booking to determine the appropriate method of delivery in the current pregnancy, even if only to seek relevant information for a firm decision to be made later in the pregnancy. Similarly, for a woman with a previous stillbirth or growth-retarded baby (<5th centile) we looked for evidence that some method to assess fetal well-being in later pregnancy had been arranged or suggested, whilst leaving the choice of method entirely to the clinician concerned.

Two further risk factors, rubella and rhesus status, are included in the study for comparison as they are checked by clerical routine as opposed to medical initiative. Where appropriate after delivery, the postnatal ward staff ensure the administration of anti-D and offer rubella vaccination.

The notes were examined independently by two doctors (F.S. and K.G.), i.e. the same 600 case-notes were reviewed twice. The findings were analysed using the name and unit number as a method of identification. Of the 600 case-notes reviewed, some contained no risk factors and some more than one. The two initial assessors (K.G. and F.S.) came to significantly different conclusions about the number of risk factors and the frequency with which they appeared to have been recognized and acted upon. A total of 311 differences of opinion occurred out of the total of 486 elicited risk factors (64%). Where differences of opinion were encountered, the notes were then scrutinized by a third doctor (F.M.). Initially, she reviewed these notes 'blind', i.e. without knowing the results of the previous two researchers. The final result was then reached by consensus following a final review of each point of difference by the two auditors. A summary of the findings of the individual researchers and subsequent audits are displayed in Table 2. Statistical analysis was by χ^2 contingency table analysis.

Results

From the final arbitration figures it was found that of 379 risk factors present at booking among 600 patients, 260 (69%) were recognized, and of these, 213 (82%) resulted in what was considered to be appropriate action. If factors 7 and 8 (rubella and rhesus status) are discounted, the number of risk factors present was 270 of which 152 (56%) were recognized and, of these, 106 (70%) were acted upon, thus 39% of the risk factors present were acted upon. The occurrence of risk factors together with the proportion recognized are listed in Table 1.

The pick-up rate of individual risk factors varied from 17 to 100%. The greatest shortfalls

Table 2. Retrospective review by three investigators of 22 selected risk factors, present, recognized, and acted on in 600 obstetric case-notes covering the years 1978–1984

Investigator	Factor present in notes	Factor recognized by doctor	Response made
F.S.	371	322	311
K.G.	410	270	215
F.M.	387	262	216
F.M. + K.G.	379	260	213

F.S. *vs* K.G. $\chi^2 = 17{\cdot}8383$, $P<0{\cdot}001$.
F.M. *vs* F.M. + K G. $\chi^2 = 0{\cdot}2262$, NS.

in performance were in factors in category 3 (Table 1).

The proportion of risk factors recognized and acted upon improved dramatically over the study period. Only 95 of the 173 risk factors present in 1978 and 1980 were recognized (55%) and 76 (79%) of those were acted upon. In 1982 and 1984, however, 165 of the 206 factors were recognized (80%) and 137 (83%) of those were acted upon. The improvement in this proportion was significant ($\chi^2 = 7{\cdot}7183$; $P<0{\cdot}05$). This improvement was most marked for the less ambiguous and most important (category 1) factors (Table 1). Deficiencies remain, however, and these are itemized in Table 3.

Rubella and rhesus status are checked routinely in the booking clinic and the results are recorded prominently on the front page of the case-notes. These results are therefore not available to the obstetrician at booking. The decision to retain a response to these risk factors when present, i.e. offer rubella vaccination or give prophylactic anti-D, is taken by the ward staff after delivery and the general practitioner is notified of this in the discharge summary. A risk factor recognition rate of 100% would therefore be expected and there should be a 100% response rate. This was the case in the 80 rhesus-negative patients. Two of the rubella non-immune patients, however, were not offered immunization. This was due to the immune status being recorded incorrectly on the front of the case-notes of one woman, and in the other vaccination was not offered on the grounds that tubal ligation was performed at the time of caesarean section in the index pregnancy.

Ethnic origin was recorded in the case-notes from 1981 onwards with consequent routine blood testing for thalassaemia and sickle cell trait where appropriate. The outcome of recording ethnic origin routinely and testing for thalassaemia was not as successful as that for rhesus and rubella status. Twenty patients appeared from their maiden names to be of Asian extraction but in two of them ethnic origin was not coded and in three others appropriate testing for thalassaemia was not offered.

Discussion

Audit has become a widely accepted and popular concept in medicine. Antenatal care is a form of population screening based on an unusually large number of risk factors. The scope for errors of omission is therefore very large. This is consequently an important area for audit and assessment of methods to improve the delivery of service.

The most complex antenatal attendance is the first or booking visit. This is the point at which the previous history is reviewed and a large amount of data must be assimilated by the clinician in a short time. Only one previous formal audit of this process has been published (Chng *et al.* 1980).

Our findings show that the quality of care at the booking visit is comparable with that reported by Chng *et al.* (1980). Nevertheless, there is room for improvement and no justification for complacency. Our findings, however, show that audit itself is a complex process. Even within the constraints of an agreed set of performance indicators there is a wide inter-observer variation. Our study therefore incor-

Table 3. Factors present which did not have 100% recognition rates (1982/84)

Category	Factor no.	Factor	Recognition rate
1	4	Mediterranean ethnic origin	67
	5	Indo-Pakistani ethnic origin	90
	6	Patient on specific drugs	80
2	10	Previous IUGR	50
	13	Recurrent cystitis	50
	14	Prevent DVT/cardiac condition	83
	16	Previous caesarean section	93
3	17	Chronic hypertension/PIH	36
	19	Previous pre-eclampsia/eclampsia	33
	20	Previous retained placenta or PPH	50
	21	Previous preterm labour	67

porated an 'audit of the audit' and we found a 64% overall disagreement between two primary observers. We recommend that future research should take this wide variation into account and include an estimate of inter-observer variation. A further problem with audit is that there is little agreement as to the optimum clinical response to any recognized risk factor. We concede that the presence or absence of 'appropriate' clinical action is difficult to judge with respect to some factors, such as chronic hypertension, and we therefore graded the various risk factors according to how unequivocally we could state the appropriate medical response.

Between 1980 and 1982 there were two major aspects of change in the antenatal clinic. One was the routine recording of ethnic origin instigated in 1981 and the other was the replacement of one consultant on retirement by two others with the additional appointment of a senior lecturer, much reducing the workload per clinic. Concurrently, between the first and second periods of the study, there was a significantly increased overall risk factor recognition and action rate. If medical performance at booking is analysed by year and category a significant improvement is notable, between the two halves of the study, 1978/1980 and 1982/1984, particularly for factors in category 1 ($P = 0{\cdot}0000003$). Thus, there was an improvement in both the total number of factors recognized and in the proportion of important and unambiguous risk factors that provoked a response.

Our study can only take into account those risk factors which were detected by the midwife's history. It has been shown in previous studies that this history is itself frequently incomplete and sometimes inaccurate. Computerized questionnaires provide a much greater level of detail than the traditional booking interview (Lilford & Chard 1981, 1983). It has been shown that an enhanced level of detail with computer-assisted diagnosis leads to better clinical decisions by doctors (De Dombal 1984). Computers may also enhance the ability of staff to respond to existing risk factors. Clinical reminders and suggestions (Lilford & Chard 1984) produced by a computer on the basis of medical details have been shown to improve the ability of doctors to respond to risk factors in a medical outpatient department (McDonald 1976). In an obstetric department, staff responded to three-quarters of the computer-generated suggestions (Lilford *et al.* 1985). It is thus possible that, in addition to conventional measures such as staff training, computer-produced reminders may greatly improve the quality of antenatal care.

We believe that other methods are less likely to produce a consistent improvement in antenatal care. It is unlikely that more detailed training will have this effect, as the omissions which we have detected are not intellectually difficult to grasp or memorize. These errors arise not from inadequate knowledge but from the inherent human difficulty of doing a repetitive task with unrelenting attention and vigilance. Peer review and the fear of litigation have a limited impact because 'man' is not perfectable and is inherently prone to errors of omission. These principles are well known in aviation where co-pilots are employed and checklists form an integral part of cockpit routine. Thus medical care in general, and antenatal care in particular, might benefit from a more rigid and disciplined system of data collection augmented by printed checklists or computerized action suggestions.

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The validity of screening for small-for-gestational-age and low-weight-for-length infants by Doppler ultrasound

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Summary. A prospective blind study assessed the efficacy of Doppler examination of the umbilical arteries (pulsatility index) as a screening procedure for predicting small-for-gestational-age and low-weight-for-length (low ponderal index) infants. Birthweight below the 2·3rd and 10th centile and ponderal index below the 3rd and 10th centile were chosen as 'cut-off' levels. Of pregnant women from our university hospital population, 400 were examined at 28 and 34 weeks gestation. The sensitivity of the test was low, ranging from 16·9 to 41·7% for the different indices. The predictive value of a negative screening test also was unsatisfactory, ranging from 79·6% to 97·9%. It is concluded that a single umbilical artery Doppler examination at 28 or 34 weeks does not satisfy the need in obstetrics for a simple and accurate technique to screen for small-for-gestational-age and low-weight-for-length infants in an unselected obstetric population.

After immaturity, low-birthweight-for-gestation is the most important variable related to perinatal complications, mortality, or subsequent neurological handicaps (Allen 1984). Therefore, a major goal of antenatal care is to identify the small-for-gestational-age (SGA) infant.

Because SGA infants can be either growth retarded or genetically small, more accurate standards are sought to improve definitions of poor fetal growth. The neonatal ponderal index (birthweight × 100/length^3) correlates better with observed neonatal problems than birthweight. The ponderal index is a body-mass-for-height ratio and therefore is a useful standard for 'intrauterine wastage' (Walther 1982).

There are difficulties both in detecting poor fetal growth antenatally and in defining the condition at time of birth. Serial fundal measurements can predict up to 50% of infants with a birthweight below the 10th centile (Rosenberg *et al.* 1982). Screening procedures with biochemical assays identify only 30% of SGA infants (Aickin *et al.* 1983; Lilford *et al.* 1983). One-point screening with ultrasound fetometry may be better; the product of crown–rump length and trunk area is reported to detect about 90% of the SGA infants in an unselected population (Neilson *et al.* 1984). These combined fetometric techniques need special sonographic skill, are time-consuming and thus restricted to well-equipped centres. Since an insufficient placental circulation could be a major cause of impaired fetal growth and because Doppler examination of the umbilical arteries enables non-invasive exploration of fetoplacental haemodynamics (Trudinger *et al.* 1985; Erskine & Ritchie 1985; Reuwer *et al.* 1984*a*, *b*, 1987) much attention is now focused on this method.

The pulsatility of flow in the umbilical arteries reflects downstream placental impedance to flow, and can be quantified by the pulsatility index (PI). The recording technique is so simple

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that Doppler examination of the umbilical arteries could become a diagnostic tool used at the bedside or in the office (Reuwer *et al.* 1984*b*).

Serial Doppler measurements might detect placental circulatory incompetence several weeks before small fetal size is clinically recognized (Reuwer *et al.* 1984*b*). Its diagnostic validity, used as a weekly monitoring tool for predicting fetal distress, has been established (Reuwer *et al.* 1987). Controlled trials to assess the clinical value are now in progress in several centres (Trudinger *et al.* 1987). However, a method with proven diagnostic validity, if used on a weekly basis in a high-risk population, is not necessarily of value in the routine screening of the general population (Grant & Mohide 1982).

This study assesses the validity of umbilical artery Doppler measurements as a screening tool at 28 or 34 weeks or on both occasions for the prediction of SGA and low-weight-for-length infants in a non-selected university hospital population. SGA was defined as birthweight below the 2·3rd or 10th centile. Infants who are underweight for length are likely to have suffered from intrauterine deprivation at the end of pregnancy. A ponderal index below the 3rd or 10th centile is taken as a measure for low-weight-for-length. Infants with both birthweight centile and ponderal index below the 10th centile are most likely to have suffered adverse intrauterine conditions and are also included in the analysis.

Subjects and methods

A random sample was taken from the university hospital population. Our obstetric department is a tertiary referral centre for the region and has a walk-in clinic as well. The study was prospective and blind. After informed consent 400 women with singleton pregnancies entered the study. Clinicians had no access to the Doppler data.

Time of screening

Gestational age was confirmed by ultrasound in early pregnancy. Doppler measurements were performed at 28 completed weeks (± 6 days), and at 34 completed weeks (± 6 days).

Doppler recordings

The women were examined in a semi-recumbent position. After the umbilical cord was identified, the echo transducer was replaced by the probe of a pulsed Doppler device (Alvar 4 MHz) held in the same direction. When the characteristic signal of the umbilical artery was obtained, it was recorded on tape, followed by off-line spectrum analysis (Doptek 9000). The recording was accepted if it showed 15 uniform flow velocity waveforms. The PI of the spectrum outline was calculated over five beats. The PI of one examination was taken as the average PI of three steady state recordings. Reproducibility of the technique was described by Reuwer *et al.* (1984*a*).

Reference values

PI reference values related to gestational age were established in a previous study of 70 uneventful pregnancies with normal outcome that had been examined every 2 weeks from the 24th postmenstrual week onwards (Reuwer *et al.* 1984*b*, 1986). The 95th centile of our reference values was used as the threshold. Abnormal low PI values seem of no clinical importance. Therefore the boundary between normal and abnormal PI values was chosen at the 95th centile (instead of the 2·3rd and the 97·7th centile) to conform to the statistical but arbitrary habit of setting bounds at 5%. The PI value of the 95th centile at 28 weeks is 1·46, and 1·27 at 34 weeks.

Standards for fetal growth

Two definitions for SGA were considered: birthweight below the 2·3rd and birthweight below the 10th centile for gestational age (Kloosterman 1970). Low-weight-for-length was defined as a ponderal index value below the 3rd and 10th centile for gestational age (Miller & Hassenein 1971). The combination of both birthweight and ponderal index below the 10th centile for gestational age was also considered.

Results

Characteristics of the study population

Our study population was a representative sample in our hospital. The prevalence of SGA in the study (birthweight 3% under the 2·3rd centile, and 22% under the 10th centile) is comparable to the rate of SGA in our hospital population (birthweight 5% under the 2·3rd centile, and 17% under the 10th centile).

Missing values

Doppler screening was performed at both 28 weeks and 34 weeks in 362 women, but 32 women were tested only at 28 weeks. Birthweight was recorded in all the 394 infants of women studied at 28 weeks. Length measurements were not adequately recorded in 42 of these, and therefore 352 had a record of ponderal index. Additional to the 362 women who attended both screening sessions, six women were tested only at 34 weeks. Birthweight was available in all 368 cases studied at 34 weeks. There were 32 women who either were delivered before 34 weeks or did not attend the screening at 34 weeks for reasons unrelated to their pregnancy. The ponderal indices of 330 infants of the women studied at 34 weeks were available.

Performance of the screening test

Validity of the data is given in Table 1.

Sensitivity and the positive predictive value of a one-point screening at 28 or 34 weeks were low for all criteria. Also the specificity and negative predictive value were unsatisfactory for all standards used. No improvement was obtained by evaluating those pregnancies with an elevated PI twice, at 28 and again at 34 weeks.

Overall, PI values at 28 or 34 weeks do not correlate with birthweight centiles, nor with ponderal index centiles. Figures 1 and 2 show the correlation plots at 34 weeks; at 28 weeks the correlation plots showed similar distributions.

Discussion

Obstetricians would like an accurate screening tool for SGA infants. Such screening must be simple and should be able to select the population at risk for SGA initiating further (serial) ultrasound measurements to reach a definitive diagnosis. To date, no simple one-point screening test can sufficiently identify the pregnancies at risk for SGA (Villar & Belizan 1986).

Fetal growth is the result of a complex interaction between intrinsic growth potential and placental competence. Placental function

Table 1. Validity of Doppler screening for SGA and low-weight-for-length infants at 28 weeks, 34 weeks or at both 28 and 34 weeks

	Sensitivity (%)	Specificity (%)	Predictive value Pos. (%)	Predictive value Neg. (%)	Prevalence
PI ≥1·46 at 28 weeks					
Birthweight ≤2·3rd centile	38·6	93·4	16·6	97·8	(13/394) 3·3%
Birthweight ≤10th centile	16·9	95·1	50·1	79·6	(89/394) 22·6%
Ponderal index ≤3rd centile	20·0	94·1	13·0	96·4	(15/352) 4·3%
Ponderal index ≤10th centile	19·4	94·9	30·4	91·2	(36/352) 10·2%
Birthweight ≤10th centile and ponderal index ≤10th centile	25·0	94·8	26·1	94·4	(24/352) 6·8%
PI ≥1·27 at 34 weeks					
Birthweight ≤2·3rd centile	41·7	91·9	14·7	97·9	(12/368) 3·3%
Birthweight ≤10th centile	22·0	94·4	52·9	80·8	(83/368) 22·2%
Ponderal index ≤3rd centile	27·3	91·5	10·0	97·3	(11/330) 3·3%
Ponderal index ≤10th centile	24·1	92·7	23·3	92·7	(29/330) 8·8%
Birthweight ≤10th centile and ponderal index ≤10th centile	33·3	92·6	23·3	95·3	(21/330) 6·4%
PI ≥1·46 at 28 weeks and ≥1·27 at 34 weeks					
Birthweight ≤2·3rd centile	8·3	98·0	12·5	96·9	(12/362) 3·3%
Birthweight ≤10th centile	7·5	99·3	75·0	79·1	(80/362) 22·1%
Ponderal index ≤3rd centile	9·1	99·7	16·7	96·8	(11/324) 3·4%
Ponderal index ≤10th centile	6·9	98·6	33·3	91·5	(29/324) 9·0%
Birthweight ≤10th centile and ponderal index ≤10th centile	9·5	98·7	33·3	94·0	(21/324) 6·5%

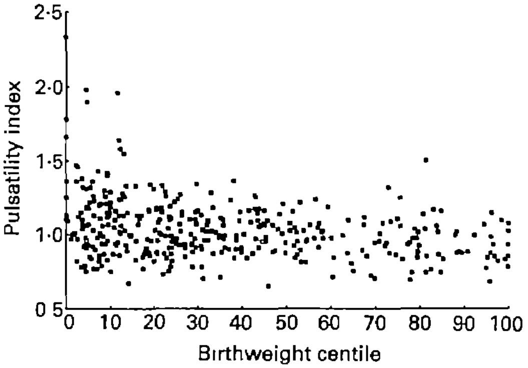

Fig. 1. Correlation plot of pulsatility index values at 34 weeks and birthweight centiles.

depends both on an adequate circulation and on nutritive transfer abilities. The relative contribution of each of these factors can not be distinguished in individual pregnancies. Recently, however, the circulatory component can be explored by Doppler ultrasound. Since an incompetent placental circulation could be a major cause of malnutrition, it was hypothesized that Doppler screening should be predictive of SGA or low-weight-for-length infants, despite lack of information on the other growth factors.

A screening procedure must be evaluated in a well-defined population in which the prevalence of the adverse condition of interest is known. It should be prospective and blind, and the test should be applied to all patients in the same week(s) of pregnancy. Until now no reported study on umbilical artery Doppler measurements has met these criteria.

Fleischer *et al.* (1985) examined umbilical artery flow velocity waveforms in 189 fetuses. They found a 78% sensitivity with a 49% predictive value of a positive test for SGA (defined as birthweight <10th centile) and a 95% predictive value of a negative test. However, almost half the population in this study belonged to a high-risk group. Moreover, serial Doppler recordings were performed between the 31st and 39th weeks, but it is not clearly stated which of these serial measurements were evaluated with respect to fetal outcome. The study of Trudinger *et al.* (1985) is also biased by the issue of serial measurements. Most of the Doppler data were ignored, and only the last test results were evaluated. This restricted analysis neglects the crucial question of how the test is to be used in actual clinical practice. The obstetrician who must interpret the Doppler result does not know when the woman will give birth and therefore cannot tell whether or not this will be the final test. The performance cf the test may change with gestational age, and also the closer the measurement is to delivery, the greater the chance for placental incompetence (higher prevalence). Evaluation of only the final Doppler measurement will overestimate the validity of the test (Grant & Mohide 1982). Our results of screening at fixed gestational ages are more disappointing.

The high frequency of infants with a birthweight below the 10th centile in our study may be explained by the organization of the Dutch obstetric service where 36% of women have an uneventful home delivery. Moreover, half the women in our population smoke cigarettes, which is predominantly related to symmetrically low-birthweight infants (d'Souza *et al.* 1981).

In an attempt to achieve high sensitivity our Doppler threshold was set at the 95th centile of our reference values. Nevertheless, the present screening results at 28 or 34 weeks show only a sensitivity of 38·6% and 41·7% respectively for infants with a birthweight below the 2·3rd centile, and 16·9% and 22·0% below the 10th birthweight centile. Considering the prevalence of SGA this is too low to be of clinical relevance.

An explanation for this poor performance might be that SGA is not always the result of an impaired fetoplacental circulation; the infant might just be genetically small. If so, screening for newborns with a low ponderal index should perform better. However, screening by this technique for infants with a ponderal index below the 3rd centile also shows low sensitivity (20·2% at 28 weeks and 27·1% at 34 weeks). If a ponderal index below the 10th centile is used as the standard, sensitivity is 19·4% at 28 weeks and 24·1% at 34 weeks. Apparently, placental function can

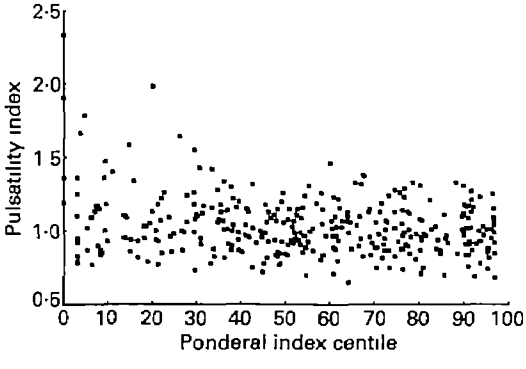

Fig. 2. Correlation plot of pulsatility index values at 34 weeks and ponderal index centiles.

be compromised despite a normal circulation, or haemodynamic measurements at 28 or 34 weeks are too early. Adverse events resulting in infants who are underweight for length, such as placental infarction, could occur later in pregnancy.

When we consider the infants who are the most likely to have suffered from poor intrauterine growth and have both birthweight and ponderal index below the 10th centile, the best sensitivity is still only 33·3% at 34 weeks.

Apparently, growth retardation can occur despite a normal fetoplacental circulation as measured by Doppler, perhaps on the basis of insufficiency of nutritive transfer (Reuwer *et al.* 1987). Because Doppler identification of an at-risk group in the 28th week is unsatisfactory (low sensitivity), no improvement can be expected of a double positive test at both 28 and 34 weeks. Indeed, sensitivity then falls to values <10% (Table 1). We conclude that umbilical artery Doppler has no future as a screening test for SGA in an unselected Dutch hospital population. However, this negative result does not devalue the technique as a potential diagnostic or monitoring tool for fetal stress or distress in high-risk pregnancies (Reuwer *et al.* 1987).

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Reactive fetal heart rate response to vibroacoustic stimulation in fetuses with low scalp blood pH

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Summary. Fetal vibroacoustic stimulation in fetuses with suspicious or ominous fetal heart rate traces in labour was followed by acid-base balance determination on fetal scalp blood within 30 min of the test. The mean fetal scalp blood pH values were significantly higher in fetuses that showed reactive responses with fetal heart rate acceleration compared with those who had no response or responded with a deceleration to the vibroacoustic stimulation (pH 7·30 and 7·22 respectively). However, acidotic scalp blood pH values (7·16 and 7·18) were found in two fetuses which had shown reactive responses both to vibroacoustic stimulation and pain stimuli with scalp blood sampling.

It is generally agreed that a reactive fetal heart rate (FHR) pattern is associated with a well-oxygenated fetus. Alternatively fetal distress is not a consistent finding when an ominous FHR pattern is recorded. In such cases determination of pH in fetal scalp blood is often recommended but problems with sampling and interpretation are not uncommon. The clinical usefulness of this method has been assessed by Clark & Paul (1985) and Ingemarsson & Arulkumaran (1986).

It is therefore of interest to find other non-invasive methods to assess fetal well-being in labours associated with suspicious or ominous FHR patterns. FHR responses with accelerations (>15 bt/min for >15 s) to various stimuli are generally regarded as reassuring. Different stimuli have been used for this purpose such as fetal scalp puncture at the time of fetal blood sampling for pH determination (Clark *et al.* 1982), application of an atraumatic clamp on the fetal scalp (Clark *et al.* 1984) and, recently, vibroacoustic stimulation (Smith *et al.* 1986; Edersheim *et al.* 1987). In these reports reactive FHR responses were always associated with a fetal scalp blood pH above the acidotic range (7·20) which is noteworthy since a pH of 7·20 is just an arbitrary cut-off point.

This preliminary study describes FHR responses to vibroacoustic stimulation of the fetus in labour. We report two fetuses with reactive FHR responses but acidotic scalp blood pH values, and we discuss the possible mechanisms for such a response.

Patients and methods

Patients subjected to fetal blood sampling because of suspicious or ominous FHR traces in the first stage of labour were recruited for the study. The traces showed late decelerations (intermittently or repeatedly), pronounced variable decelerations (depth >60 bt/min or lasting for >60 s or both), tachycardia with late or variable decelerations or reduced variability (<5 bt/min lasting for >60 min) indicative of possible fetal acidosis. Before fetal blood sampling the fetus was stimulated vibroacoustically. A model 5C Electronic Artificial Larynx (EAL: Western Electric, Bell Telephone) was applied

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to the maternal abdomen in the region of the fetal head for 5 s. A response was defined as reactive if the FHR showed an acceleration of 15 bt/min for 15 s immediately after the sound stimulation. Fetal scalp blood for determining the acid-base balance (pH, $P\text{CO}_2$, HCO_3 and standard HCO_3) was taken by one of the authors (S.A.) within 20 min of sound stimulation with the patient in the left lateral position. Cord artery blood was taken at caesarean section in 15 patients when scalp blood sampling was not possible due to high head and inadequate dilatation of the cervix.

The pH was considered low at a value of ≤7·25 in scalp blood and <7·16 in cord artery blood. 'Pre-acidosis' was defined as a pH value in the range 7·20–7·25 and acidosis as a pH value <7·20. Fetal respiratory acidosis was defined by an elevated $P\text{CO}_2$ level and a bicarbonate value within normal range. Elimination of excessive fetal CO_2 can only occur through the mother, and in labour this may be influenced by changes in placental circulation, uterine contractions and possible cord compression, all of which may complicate the interpretation (Rooth 1987).

Results

Fifty-one women at between 35 and 42 weeks gestation were recruited to the study. Cervical dilatation ranged from 1 to 9 cm. A reactive FHR response to vibroacoustic stimulation was recorded in 29 of them (57%). Table 1 shows the mean pH values in scalp or cord artery blood.

No response or a deceleration of the FHR was observed in 22 patients (43%). The mean pH values both in scalp and cord artery blood in this group were significantly lower than in those who had a reactive FHR response. The mean scalp blood pH value in the group with no response or a deceleration was 7·22, in the pre-acidotic range. Of the 22 fetuses without a response or FHR deceleration, 13 (59·1%) had a low pH either in scalp or cord artery blood. In the reactive group all but two fetuses had a normal pH (Fig. 1).

In the whole study group 11 fetuses had pre-acidotic and acidotic pH values in scalp blood and their details are listed in Table 2. Four had a scalp blood pH <7·20; two of them showed a reactive FHR response to vibroacoustic stimulation (5 and 20 min before scalp blood sampling), one showed a deceleration for more than 2 min, and the fourth showed no response. There was no FHR response to vibroacoustic stimulation in the seven fetuses with pre-acidotic pH values. In nine of these 11 fetuses FHR response to fetal blood sampling could be assessed. Six showed an acceleration including the two fetuses that showed acidotic pH values and reactive responses to vibroacoustic stimulation.

An analysis of the acid-base balance showed that pre-acidosis or acidosis were predominantly of the respiratory type with $P\text{CO}_2$ values >3·98 kPa, HCO_3 values >20·5 mmol/l, and standard HCO_3 >17·6 mmol/l in all cases. All but two of the 11 patients were delivered by caesarean section. Apgar scores were <4 at 1 min in three (nos 3, 4, 8) and <7 at 5 min in one (no. 5).

Discussion

A simple non-invasive 'stimulation' test to induce FHR reactivity in a suspicious or an ominous intrapartum FHR trace, particularly where there is poor variability for a period lasting >60 min, would be of clinical value and may reduce the need for scalp blood sampling. Published reports to date agree that a fetus that reacts with an acceleration to various stimuli does not have acidotic blood pH values. Clark *et al.* (1984) concluded that FHR response to digital pressure on the head or to a gentle pinch on

Table 1. Number of patients and mean pH values in scalp or cord artery blood in relation to FHR responses to vibroacoustic stimulation

		Scalp blood pH		Cord blood pH	
FHR response	*n*	No. sampled	Mean (SD)	No. sampled	Mean (SD)
Reactive response	29	22	7·30 (0·06)	7	7·28 (0·06)
No response or deceleration	22	11	7·22 (0·05)	11	7·18 (0·11)

The differences in pH values within the two groups (scalp blood and cord) are statistically significant $P<0{\cdot}001$ and $P<0{\cdot}05$, respectively (Student's *t*-test, unpaired observations)

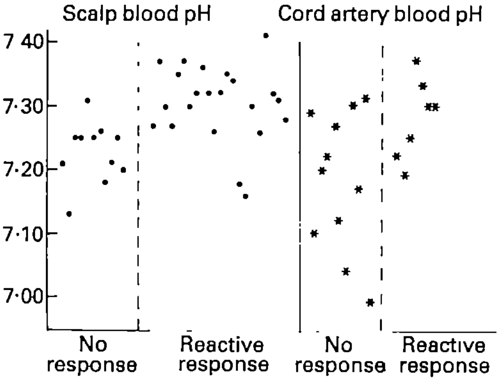

Fig. 1. Fetal scalp blood pH values in labour and cord artery blood pH values at birth in relation to fetal heart rate responses to vibroacoustic stimulation.

the scalp with an atraumatic clamp was associated with a scalp blood pH >7·19. Similar results were reported by Clark *et al.* (1982) who found pH values >7·20 in all fetuses which responded with an acceleration to scalp blood sampling. In a recent study, Smith *et al.* (1986) reported that the presence of FHR accelerations to vibroacoustic stimulation was associated with scalp blood pH values >7·25 in all fetuses with ominous FHR traces. In contrast, when no FHR response was observed, half the fetuses had normal scalp blood pH values, suggesting that only the reactive FHR response can be used as a predictor of fetal well-being. Edersheim *et al.* (1987) found a scalp blood pH of >7·20 in all fetuses responding with FHR accelerations to vibroacoustic stimulation or fetal scalp puncture.

In the present study we found significantly higher pH values in fetuses responding with FHR accelerations to vibroacoustic stimulation than in those not responding at all or with a FHR deceleration. However, two of the 29 fetuses with reactive responses had acidotic pH values of 7·162 and 7·180. Keeping in mind that a fetal scalp blood pH of 7·20 is just an arbitrary cut-off point, the type of acidosis should also be considered. An analysis of the acid-base balance showed that both fetuses had acidosis of the respiratory type (Table 2).

Respiratory acidosis is generally believed to be innocuous, unless pronounced or prolonged, compared with metabolic acidosis. It has been previously reported that transient acidosis is not uncommon during labour (Ingemarsson & Arulkumaran 1986). In a low-risk population, acidotic or pre-acidotic scalp blood pH values were obtained in 9 out of 120 patients, in most cases of a respiratory, innocuous type and without any apparent cause.

Bruns *et al.* (1963) showed in animal experiments that rabbit fetuses were vigorous at birth after 90 min of induced respiratory acidosis but severely depressed after 30 min of acute metabolic acidosis. One may speculate that some fetuses with respiratory acidosis might not be depressed to an extent that an arousal reaction to external stimuli is impaired. Since it is not clear by which pathways vibroacoustic stimulation mediates fetal heart rate accelerations, the appearance of such a response after external stimulation to indicate fetal health should not be accepted unconditionally. It is notable that the two acidotic fetuses with reactive FHR responses to vibroacoustic stimulation also

Table 2. Acid-base balance in 11 patients with low scalp blood pH (<7·25) and FHR responses to sound stimulation and scalp blood sampling

Patient number	pH	$P\text{co}_2$ (kPa)	HCO_3 (mmol/l)	Standard HCO_3 (mmol/l)	FHR response to sound stimulation	FHR response to scalp blood sampling
1	7·13	5·29	22·6	17·9	Deceleration	No response
2	7·16	4·86	22·5	18·1	Reactive	Reactive
3	7·18	4·34	20·9	17·7	No response	No response
4	7·18	4·17	20·5	17·6	Reactive	Reactive
5	7·20	4·11	21·0	18·2	No response	Reactive
6	7·21	4·45	22·8	19·1	No response	Reactive
7	7·21	4·52	23·7	19·9	No response	No response
8	7·24	4·44	24·3	20·8	No response	Reactive
9	7·25	4·81	26·7	22·2	No response	NA
10	7·25	4·36	24·6	21·1	No response	Reactive
11	7·25	4·01	23·2	20·4	No response	NA

NA, Not possible to assess.

showed accelerations at scalp blood sampling. Indeed Clark *et al.* (1982) found that within the pH range 7·21–7·28 most fetuses (73%) responded with accelerations when scalp blood was sampled. Even if it was not stated one can assume that a considerable number of these fetuses had pH values within the pre-acidotic range.

In this series 11 fetuses (Table 2) had a low scalp blood pH (<7·25) predominantly of the respiratory type with high $P\text{CO}_2$ levels and normal bicarbonate levels. One baby with a pH 7·13 responded with a deceleration to sound stimulation. It has been previously suggested that such a reaction from a fetus with a non-reactive trace may be an ominous sign (Goodlin & Schmidt 1972; Ingemarsson *et al.* (1988). The other 10, however, had a mild acidosis or pre-acidosis with scalp blood pH values between 7·15 and 7·25.

Though intrapartum vibroacoustic stimulation appears to be useful, further investigations are required to study the fetal FHR responses to 'stimulation tests' in the presence of different types of fetal acidosis.

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Maternal perception of sound-provoked fetal movements in low-risk pregnancies during the third trimester

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Summary. Maternal perception of fetal movements after vibroacoustic stimulation (Servox) was studied longitudinally on 456 occasions in 90 low-risk pregnancies after 28 weeks gestation until delivery. A positive response to sound stimulation, recorded as a fetal movement by the mother, occurred on 444 (97%) occasions. Of the 12 negative responses eight occurred before 33 weeks showing a positive correlation with decreasing maturity. All the pregnancies had good outcomes. The low rate of false-positive tests (3%) adds support to the suggestion that this rapid test could play a role in the assessment of fetal well-being.

Recently, sound, or more accurately vibroacoustic stimulation of the fetus with an electric artificial larynx (EAL), has gained considerable attention. Birnholz & Benacerraf (1983) reported that EAL stimulation led to a consistent fetal blink–startle response. Divon *et al.* (1985) studied the fetal startle reflex at EAL stimulation and suggested that assessment of this generalized paroxysmal fetal reaction could be a way to assess fetal neurological status. In a previous study of high-risk pregnancies we have suggested that maternal perception of fetal movements (FM) at EAL stimulation might be used to assess fetal well-being (Westgren *et al.* 1987). The aim of the present study was to investigate this test in normal pregnancies.

Subjects and methods

Maternal perception of EAL-provoked fetal movements was studied longitudinally after 28 weeks gestation until delivery in 90 low-risk pregnancies. The test was performed by the midwife, at the routine antenatal visits, biweekly until 35 weeks gestation, and thereafter on a weekly basis.

The test procedure was the same as described previously by Westgren *et al.* (1987). The woman was resting in a semi-recumbent position. The EAL stimulation was given for 1–2 s with a hand-held EAL (Servox). The disc was applied firmly to the maternal abdomen and during the stimulation the woman was asked if she felt fetal movements. A kick immediately after the stimulation was considered a positive test response. If the woman did not feel any movements the test was repeated twice within 30 s. If no fetal movements were experienced or if the woman was not sure, the test was considered negative.

The data were analysed using Student's *t*-test. $P<0{\cdot}05$ was regarded as significant.

Results

The 90 women underwent a total of 456 tests. A positive test was recorded on 444 (97%) occasions. The 12 negative tests were recorded in six of the 90 women (6·5%). Table 1 shows the test results by gestational age. Negative tests occurred significantly more often between 29 and 33 weeks than at later gestations ($P<0{\cdot}05$).

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Table 1. Maternal perception of sound-provoked fetal movements in relation to gestational age

	Gestational age (weeks)		
Results of test	29–33	34–37	38–41
Positive	134	193	117
Negative	8	2	2
Total	142	195	119

Of the 90 women, 79 were delivered spontaneously without any complication. Four were delivered by ventouse, two due to slow labour and two due to signs of fetal asphyxia. The remaining seven patients were delivered by caesarean section, five because of cephalo-pelvic disproportion, one because of signs of asphyxia, and the last patient was delivered preterm due to maternal intestinal obstruction at 34 weeks. All pregnancies had favourable outcomes with Apgar scores >7 at 1 and 5 min.

Discussion

The present study indicates that EAL stimulation is almost always associated with maternal perception of fetal movements in low-risk pregnancies during the last trimester. Fetal ability to respond consistently with movements to vibrotactile stimulation has been documented previously (Leader *et al.* 1982; Birnholz & Benacerraf 1983), but the high rate of perception of these movements found in our study has not been reported previously. The high perception rate is comparable to the rate of maternal perception of spontaneous fetal movements reported to be in the range of 31–81%, depending on methods of recording and type of fetal movements (Schmidt *et al.* 1984). Generally, subjective maternal perception of fetal movements increases with the number of fetal parts moved, and since the startle response involves movements of all limbs, this factor might contribute to the high perception rate. In addition, it seems that the sound-provoked movement which is a generalized paroxysmal motion consisting of flexion of arms, extension of legs, and aversion of the head, is a more vigorous movement than a spontaneous fetal movement, and therefore more easily recognized by the mother. The high perception rate could be due also to maternal bias since the woman is aware that she is supposed to feel fetal movements at stimulation. Since there was no objective recording of fetal movements in the present study, the influence of this factor cannot be assessed.

Our data agree with previous reports that fetal response to vibratory stimulation is affected by gestational age. Birnholz & Benacerraf (1983) showed that the fetal eye-blink response was inconsistent before 28 weeks, but thereafter it occurred consistently. Gagnon *et al.* (1987) reported increased gross fetal body movements 1 h after EAL stimulation after 33 weeks gestation but not before. Thus, fetal response to vibratory stimulation seems to be affected by gestational age, and this must be considered when assessing fetal response to EAL.

Previously (Westgren *et al.* 1987), we have suggested that maternal perception of EAL-provoked fetal movements could become a useful first-line screening test for fetal well-being. Our low rate of false-positive tests (3%) would support this suggestion, but further studies with neurological and auditory follow-up of larger groups of exposed fetuses are required before the method is used in clinical practice.

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Are leukotrienes involved in human uterine contractility?

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Summary. The effects of leukotrienes (LT) on the contractility of human and rat myometrial strips *in vitro* were compared with the effects of prostaglandins (PGs) and oxytocin. Preparations of human myometrial membranes were investigated for the presence and characteristics of LTC_4 receptors. Neither the peptido-leukotrienes (LTC_4, LTD_4, LTE_4) nor LTB_4 had any consistent effect, stimulatory or inhibitory, on human pregnant or non-pregnant myometrium, at doses up to 1·25 μM; nor did they have any effect in rat non-pregnant myometrium. As expected, PGE_2, $PGF_{2\alpha}$ (0·3 μM) and oxytocin (5 nM) stimulated human pregnant myometrium. $PGF_{2\alpha}$ stimulated and PGE_2 inhibited human non-pregnant myometrium but oxytocin had no effect; all three compounds stimulated rat non-pregnant myometrium. The binding of ^3H-LTC_4 to human myometrium was specific ($LTC_4 > LTD_4 >>> LTE_4$, LTB_4, PGE_2, $PGF_{2\alpha}$, arachidonic acid) but of low affinity compared with the binding of ^3H-PGE_2 to the same membrane preparations. These data support the view that leukotrienes have little direct influence on myometrial contractility.

Leukotrienes are 5-lipoxygenase metabolites of arachidonic acid with potent biological effects in several organs. The sulphidopeptide leukotrienes (LTC_4, LTD_4, LTE_4) stimulate smooth muscle contractility in the gastrointestinal, pulmonary and cardiovascular systems (Piper 1984), but their action on the uterine musculature is not well understood. LTB_4 is a potent chemotactic agent involved in inflammatory reactions; it has few direct muscle-stimulating actions, but it is possible that it contributes indirectly because it can mobilize calcium and stimulate phospholipase A_2 activity leading to prostaglandin formation (Piper 1984; Lewis & Austen 1984).

LTC_4, LTD_4 and LTE_4 are released by endometrium and myometrium throughout the menstrual cycle (Rees *et al.* 1987) and by placenta, fetal membranes and decidua in pregnancy (Rees *et al.* 1988), so it is possible that these compounds have a direct local effect on uterine activity. LTB_4 is produced by amnion and placenta and its concentration increases in amniotic fluid in women with intrauterine infections (López Bernal *et al.* 1987; Romero *et al.* 1987*a*), thus raising the possibility that it may be involved in the onset of preterm labour in chorioamnionitis.

In this paper we have investigated the effect of leukotrienes on human myometrial contractility *in vitro*, and in comparison with well-known agonists such as oxytocin and prostaglandins. We have also detected LTC_4 'receptors' in human myometrium and compared their binding

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1 characteristics with those of the well-described myometrial prostaglandin E (PGE) receptor.

Materials and methods

Myometrium was collected from the lower uterine segment in seven pregnant women at elective caesarean section at term, and from the uterine corpus in four premenopausal women at hysterectomy. Caesarean sections were indicated for previous section, malposition or malpresentation, and were conducted under general or epidural anaesthesia. All women were delivered of healthy singleton infants and there were no medical complications of pregnancy. Hysterectomies were indicated for gynaecological reasons: menorrhagia and dysmenorrhoea; two were performed in the mid-follicular and two in the mid-luteal phase of the menstrual cycle. The tissues were collected in accordance with the requirements of the Central Oxfordshire research ethics committee. Uterine horns were obtained from two mature non-pregnant rats.

Contractility experiments

Strips of myometrium of 2–3 mm diameter and 10–15 mm length (approximately 100 mg wet weight) were suspended in 5-ml organ baths, superfused with oxygenated (95% O_2–5% CO_2) Krebs solution at 35°C. The strips were attached to a strain gauge at a resting tension of 10 mN and isometric contractions were recorded. The mM composition of the Krebs solution was: NaCl 126·1, KCl 4·7, $MgSO_4$ 1·1, KH_2PO_4 1·2, glucose 2·8, $NaHCO_3$ 25, $CaCl_2$ 1·3. Three strips of myometrium per patient were superfused in parallel. The tissues were allowed to equilibrate for 1 h and then were stimulated with repeated doses (5 μM) of 5-hydroxytryptamine (5-HT). Strips that failed to respond consistently to 5-HT were discarded. All viable tissues developed spontaneous contractility. The tissues were then exposed to increasing concentrations (0·05, 0·25, 1·25 μM) of LTB_4, LTC_4, LTD_4 and LTE_4 and then prostaglandins ($PGF_{2\alpha}$, PGE_2; 0·3 μM) and/or oxytocin (5, 50 nM; 2·5, 25 m-i.u./ml). The tissues were exposed to the drugs for 2–10 min, and then the medium was washed out by 2 upward displacement with fresh Krebs solution. Each compound was tested on tissues from at least three different patients.

Binding experiments

These were carried out as has been described elsewhere (Adelantado *et al.* 1988), with the following modifications. Homogenates of myometrium were prepared in 50 mM Tris-HCl buffer, pH 7·4, containing either 10 mM $MgCl_2$, 5 mM serine and 10 mM sodium borate (for LTC_4 binding) or 250 mM sucrose, 0·5 mM $CaCl_2$ and 1 mM dithiothreitol (for PGE_2 binding). The homogenates were centrifuged at 1000 *g* for 15 min and the supernatants at 50 000 *g* for 60 min. The resulting membrane pellets were washed and resuspended in the corresponding buffer and incubated with ^3H-LTC_4 (0·1–10 nM; 20 min at 4°C) or ^3H-PGE_2 (0·1–10 nM; 45 min at 20°C); parallel incubations were carried out in the presence of a 300–1000-fold excess of non-labelled eicosanoid to estimate non-specific binding. The average coefficient of variation of triplicate estimations was 7%.

LTB_4, PGE_2 and $PGF_{2\alpha}$ were gifts from Messrs S. Thomas and B. Godman, Upjohn Ltd; LTC_4 and LTD_4 were purchased from ICN Biomedicals Ltd; LTE_4 was purchased from Sigma Chemical Co. Ltd as methylester and was hydrolysed following the manufacturer's instructions. Stock solutions (1 mM in ethanol) of eicosanoids were prepared in light-proof containers on the day of use, and were diluted in buffer and kept in ice until immediately before addition to the organ bath. The biological activity of the peptidoleukotrienes was checked using the guinea-pig ileum assay. Oxytocin (Syntocinon 1 i.u./ml) was obtained from Sandoz Pharmaceuticals. Radiolabelled LTC_4 and PGE_2 (1·4 and 5·9 TBq/mmol, respectively) were purchased from Amersham International plc.

Results

Effect on contractility

Human pregnant myometrium. In tissues from six pregnant women, constant responses to 5-HT were elicited, but none of the leukotrienes tested had any stimulatory effect in any of the doses used. Both PGE_2 and $PGF_{2\alpha}$ had stimulatory effects of similar intensity at 0·3 μM. Tachyphylaxis usually occurred when the doses of PG were repeated at 15-min intervals. The tissues responded powerfully and consistently to 5 nM oxytocin, and tachyphylaxis was rare. PGs and oxytocin maintained their stimulatory effect

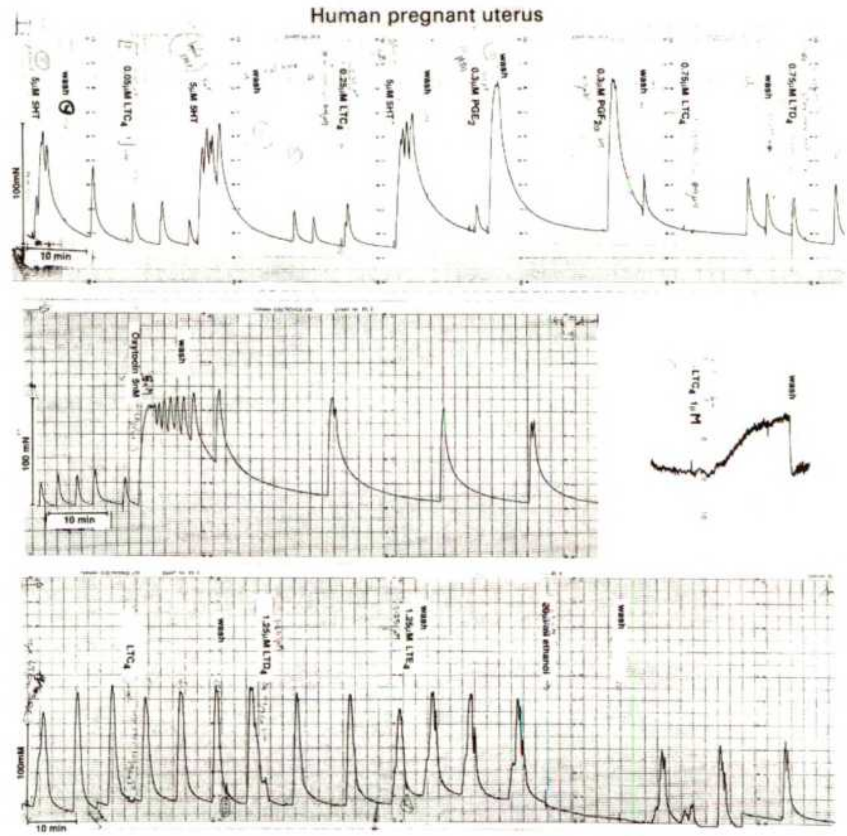

Fig. 1. Contractility of human term myometrium *in vitro*. Note the lack of stimulatory (top panel) or inhibitory (bottom panel) effects of leukotrienes (LTs) (0·05–1·25 μM). PGE$_2$, PGF$_{2\alpha}$ (0·3 μM; top panel) and oxytocin (5 nM; middle panel) were stimulatory; ethanol (0·3 mM; bottom panel) abolished spontaneous contractility. The inset in the middle panel shows the response of guinea-pig ileum to 1 μM LTC$_4$.

in the presence of 1·25 μM LTC$_4$ or LTD$_4$ and leukotrienes had no inhibitory effect on spontaneous contractility at doses up to 1·25 μM. Contractility, however, was readily abolished with ethanol (0·3 mM). Typical tracings are shown in Fig. 1.

Human non-pregnant myometrium. Constant responses to 5-HT were obtained in myometrial strips from the four patients studied. No consistent effects, either stimulatory or inhibitory, were observed with any of the leukotrienes in the dose range tested (Fig. 2), although high doses (2·5 μM) of LTC$_4$ caused mild inhibition of spontaneous contractility in strips from two uteri. PGF$_{2\alpha}$ and PGE$_2$ at a dose of 0·3 μM had consistent but opposite effects: PGF$_{2\alpha}$ stimulated and PGE$_2$ inhibited contractility (Fig. 2). As with pregnant myometrium, tachyphylaxis occurred when the doses of PG were repeated at 15-min intervals. None of the tissues responded to oxytocin (50 nM).

Non-pregnant rat myometrium. Myometrial strips from two different rats were exposed to LTC$_4$ and LTD$_4$ (0·5–1·25 ng/ml) but no effect, stimulatory or inhibitory, was observed. However, the tissues responded consistently and in a dose-dependent manner to PGE$_2$, PGF$_{2\alpha}$ and oxytocin; all three compounds had stimulatory effects (Fig. 2).

Binding experiments

Membrane preparations from two pregnant and two non-pregnant patients were studied. As expected from previous findings (Carsten & Miller 1981; Adelantado *et al.* 1988), PGE$_2$ binding was of high affinity [Kd 0·6 (SD 0·1) nM, $n=4$] and saturable at about 4 nM, whereas LTC$_4$ bind-

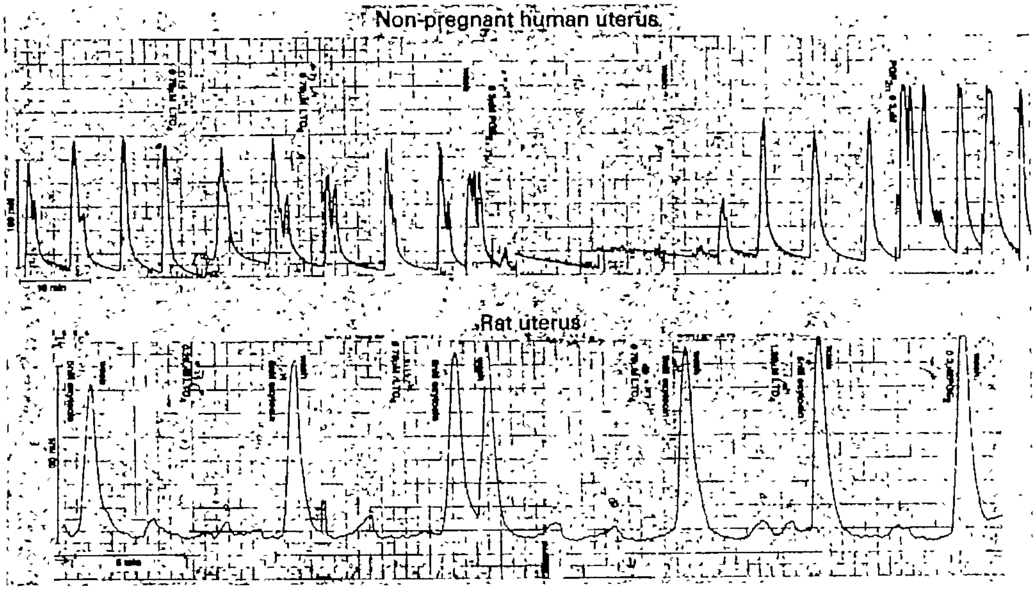

Fig. 2. Contractility of human (top panel) and rat (bottom panel) myometrium *in vitro*. Leukotrienes (0·05–1·25 μM) had no effect, either stimulatory or inhibitory in any tissue. PGE_2 (0·3 μM) inhibited and $PGF_{2\alpha}$ (0·3 μM) stimulated human myometrium. Oxytocin (5 nM) and PGE_2 (0·3 μM) stimulated rat myometrium

ing was of low affinity (Kd>8 nM; Fig. 3). For competition experiments 10 nM ^3H-LTC_4 was incubated in the presence, and in the absence, of 10 μM non-labelled eicosanoid. Total binding was decreased by 75% and 30% by LTC_4 and LTD_4, respectively, whereas LTB_4, PGE_2, $PGF_{2\alpha}$ and arachidonic acid had no measurable effects. These data demonstrate that the binding sites detected were specific for LTC_4.

Discussion

This study has shown that, under the conditions used, neither the peptido-leukotrienes nor LTB_4 have any direct effect on human myometrial contractility *in vitro*. In myometrial strips from pregnant patients at term and non-pregnant patients, the response to PGs and oxytocin was as described by previous workers: oxytocin was a potent agonist of term pregnant myometrium but had no effect on non-pregnant tissue (Fuchs & Fuchs 1963; Wikland *et al.* 1982); PGE_2 and $F_{2\alpha}$ were both stimulatory in pregnant tissues but had opposite effects in non-pregnant myometrium (Embrey & Morrison 1968; Wikland *et al.* 1982).

There have been few studies of the effect of leukotrienes and other lipoxygenase products on human myometrial contractility. Bryman *et al.* (1985) showed that LTC_4 had no effect, stimulatory or inhibitory, on strips from the upper or lower uterine segments at term, but reported inhibition of spontaneous contractility in strips from human cervix. Bennett *et al.* (1987*a*) found no effect of LTB_4 on strips from human lower uterine segment, but noted that 5-hydroxy-eicosatetraenoic acid had stimulatory activity approximately 10 times lower than $PGF_{2\alpha}$. In

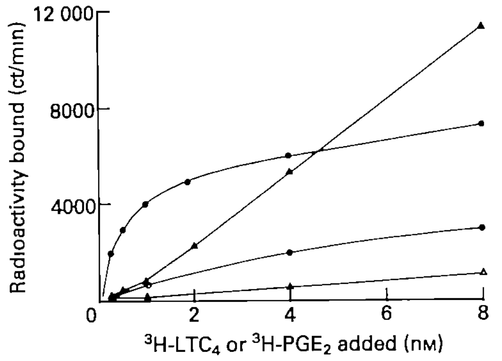

Fig. 3. Binding of ^3H-LTC_4 and ^3H-PGE_2 by human pregnant myometrium as a function of ligand concentration Incubation conditions as described in the text. The results are representative of four different experiments. ▲, ^3H-LTC_4 total binding; ●, ^3H-PGE_2 total binding; △, ^3H-LTC_4 non-specific binding; ○, ^3H-PGE_2 non-specific binding

animals, Weichman & Tucker (1982) reported stimulatory effects of LTC_4 and LTD_4 on guinea-pig uterus *in vitro,* at doses nearly two orders of magnitude higher than the dose of PGE_2 required to obtain the same effect. In the same species, Carraher *et al.* (1983) reported a possible contributory effect of leukotrienes to histamine-induced uterine contractions. These previous studies, and our own experiments with human and rat myometrium, suggest that of all the arachidonic acid metabolites tested in several species the primary prostaglandins are the strongest agonists and that leukotrienes have little or no oxytocic action.

The contractility data are supported by the binding data. High-affinity (Kd 1 nM) PGE binding sites are readily demonstrable in human myometrium and these sites are compatible with the presence of PG receptors (Carsten & Miller 1981; Adelantado *et al.* 1988). Binding sites specific for LTC_4 are also present in the same membrane preparations, but their affinity is at least 10 times lower than that of the PGE receptor. Levinson (1984) has described LTC_4 receptors in guinea-pig uterus with Kd of about 10 nM. It is difficult to say without further purification whether these LTC_4 binding sites represent true receptor proteins or enzymes such as glutathione transferase (Sun *et al.* 1987) or gamma-glutamyl transpeptidase (Rees *et al.* 1987). The presence of binding sites on vascular, connective tissue and other non-smooth muscle cells should also be considered.

The spontaneous onset of labour at term is associated with increased mobilization of arachidonic acid from the fetal membranes and it is now known that these tissues have active cyclo- and lipoxygenase pathways (Mitchell 1986; Bennett *et al.* 1987*b*). Both cyclo- and lipoxygenase metabolites increase in amniotic fluid in spontaneous labour at term (Romero *et al.* 1987*b*). In pathological situations, such as preterm labour complicated by chorioamnionitis, there is an increased output of PG and leukotrienes by the amnion because of the presence of activated inflammatory cells (López Bernal *et al.* 1987). However, the data presented here suggest that leukotrienes have little direct influence on uterine contractility and that prostaglandins are more important agents for the initiation of labour.

Women complaining of severe primary dysmenorrhoea also have increased endometrial peptido-leukotriene output throughout the menstrual cycle (Rees *et al.* 1987), but this seems unlikely to explain the uterine hypercontractility in this disorder. Nevertheless, further work is warranted to clarify whether leukotrienes modulate the response of the non-pregnant myometrium to endogenous agonists such as vasopressin (Stromberg *et al.* 1983).

Acknowledgments

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Serum CA 125 in acute pelvic inflammatory disease

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Summary. Serum levels of CA 125 and other selected tumour markers were measured in 31 patients with proven pelvic inflammatory disease (PID). Ten (32%) of the patients had elevated CA 125, one (4%) had elevated CEA, and none had elevated CA 15-3, AFP or β_2-microglobulin. Compared to patients with normal CA 125, patients with elevated CA 125 were older, more often users of intrauterine contraceptive devices, had longer duration of symptoms, higher erythrocyte sedimentation rates, and more often had an adnexal mass on pelvic examination. There was a correlation between CA 125 levels and the severity of adnexal inflammation as defined by laparoscopy. Isolation of specific micro-organisms from the upper genital tract was not associated with elevated CA 125. In most women serum levels of CA 125 decreased during treatment. PID should be considered as a major cause of positive CA 125 findings among young women.

The tumour antigen CA 125, a glycoprotein identified by monoclonal antibody OC-125 (Bast *et al.* 1981), has been extensively studied in the diagnosis and monitoring of epithelial ovarian carcinoma (Lambert 1987; Bast *et al.* 1983). The specificity of CA 125 for epithelial ovarian carcinoma has, however, been questioned as this antigen is also associated with ovarian tumours other than epithelial, and with other carcinomas (Niloff *et al.* 1984*a*; Cruickshank *et al.* 1987; Meier *et al.* 1987). Recently, elevated CA 125 levels have been reported in benign gynaecological conditions (Barbieri *et al.* 1986; Niloff *et al.* 1984*b*), thus precluding CA 125 determination as a cancer screening test among asymptomatic populations. Halila *et al.* (1986) found elevated CA 125 levels in 33% of patients with pelvic inflammatory disease (PID), but their diagnoses were based in most cases on clinical criteria known to have poor sensitivity and poor predictive value in the diagnosis of PID (Jacobson & Weström 1969; Paavonen *et al.* 1987).

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We studied serum levels of CA 125 and of other tumour markers in patients with or without proven PID, and correlated the CA 125 levels with the severity of the upper genital tract infection and with microbiological and other findings.

Patients and methods

The study population consisted of 31 women with acute PID seen at the Department of Obstetrics and Gynaecology, University Central Hospital, Tampere, between June 1983 and June 1984. The control group consisted of 10 women who underwent laparoscopic tubal ligation and had no evidence of PID. All women were admitted to the hospital, and underwent laparoscopy and endometrial sampling as described (Paavonen *et al.* 1987).

During gynaecological examination the presence of cervical excitation, uterine, or adnexal tenderness was determined. A clinical severity score was determined as described by Paavonen *et al.* (1987).

Collection of specimens

Culture specimens for isolation of *Chlamydia trachomatis, Neisseria gonorrhoeae, Mycoplasma hominis, Ureaplasma urealyticum,* herpes simplex virus, anaerobic and facultative bacteria were taken from the cervix, endometrium, fallopian tubes, and posterior cul-de-sac. If an intrauterine contraceptive device (IUCD) was present it was removed. Vaginal specimens were obtained for culture of *Gardnerella vaginalis, Trichomonas vaginalis,* and yeasts. Vaginal wash samples and endometrial, tubal and cul-de-sac specimens were obtained as described by Paavonen *et al.* (1987). Endometrial biopsy specimens were fixed in formalin and processed by routine histological methods. Acute phase sera were obtained on admission, and convalescent phase sera were taken at discharge. Paired sera were available from all but one patient.

Microbiological studies

The procedures for the isolation of specific micro-organisms have been described previously by Paavonen *et al.* (1987) and Heinonen *et al.* (1985*a*). Vaginal wash samples were analysed for volatile and non-volatile organic fatty acids by gas-liquid chromatography (GLC) using a Carlo Erba Fractovap 4200 gas chromatograph as described by Paavonen *et al.* (1986, 1987).

Biochemical studies

Assays for CA 125, CA 15-3, CEA, AFP and β_2-microglobulin (β_2M) used commercially available radioimmunoassay (RIA) kits (CIS International, France) as described previously (Heinonen *et al.* 1985*b*; Ashorn *et al.* 1988; Aaran *et al.* 1988; Lehtinen 1988). The cut-off levels (mean +2 SD) for a positive sample were determined by using a collection of serum samples from 100 healthy women aged between 25 and 75 years (mean 55 years). The cut-off levels were 30 µg/l for CA 125, 30 µg/l for CA 15-3, 3 µg/l for CEA, 30 µg/l for AFP and 2·5 µg/l for β_2M.

Serum CRP levels were determined by a turbidimetric method (Lehtinen *et al.* 1986*a*).

Definition of endometritis and salpingitis

The histopathological diagnosis of endometritis was based on the identification of plasma cells. In all cases the presence of plasma cells was confirmed with methyl green-pyronin and immunoperoxidase staining (Paavonen *et al.* 1987; Lehtinen *et al.* 1986*b*). The absolute number of plasma cells present in tissue section was counted with a semi-automated morphometry system with a graphic table as described (Paavonen *et al.* 1987). Lymphoid follicles were defined as rounded follicular accumulation of large transformed lymphocytes and recorded as present or absent. The presence of salpingitis was assessed using laparoscopic criteria of mild, moderate and severe salpingitis as described previously (Jacobson & Westrom 1969; Paavonen *et al.* 1987). The minimum criteria for salpingitis included the presence of erythema and oedema of the fallopian tubes, with mucopurulent exudate expressed from the fimbrial end of the tubes.

Statistical analyses

χ^2-test, Fisher's exact test, or Mann–Whitney *U*-test were used for statistical comparisons. Spearman's correlation coefficient was calculated and tested for significance.

Results

Of the 31 patients with proven PID, 10 (32%) had elevated CA 125 levels, one (4%) had elevated CEA level, and none had elevated CA 15-3, AFP or β_2-microglobulin levels. None of the controls had elevated CA 125 levels. Compared to patients with normal CA 125 levels, patients with elevated CA 125 levels were older ($P<0{\cdot}01$), more often IUCD users ($P<0{\cdot}05$), less often birth control pill users ($P<0{\cdot}05$), had longer duration of symptoms ($P<0{\cdot}05$), had higher erythrocyte sedimentation rates ($P<0{\cdot}01$), and more often had an adnexal mass on pelvic examination ($P<0{\cdot}01$) (Table 1).

As shown in Fig. 1, there was a correlation between the CA 125 levels and the severity of salpingitis detected at laparoscopy ($r=0{\cdot}57$, $P<0{\cdot}01$). Of five patients with severe salpingitis, four (80%) had elevated CA 125 levels. The corresponding proportions among those with moderate and mild salpingitis were four of eight (50%) and two of 14 (14%), respectively, whereas none of four patients with endometritis but no salpingitis had elevated CA 125 levels.

We also studied the correlation between CA 125 levels and histopathology of the endometrium. CA 125 was elevated in seven of 12 (58%) patients with severe endometritis, but in only 3 of 16 (19%) patients with mild to moderate endometritis and in none of three patients with no histopathological evidence of endometritis. However, when we adjusted for the severity of salpingitis there was no longer correlation between CA 125 and the severity of endometritis (data not shown). Patients with elevated CA 125 levels tended to have higher mean numbers of plasma cells in the endometrium (991, SD 1074 *vs* 485, SD 745) but the difference was not statistically significant. Furthermore, no association was seen between CA 125 and the presence of lymphoid follicles in the endometrium.

As shown in Table 2, there was no correlation between the isolation of specific micro-organisms from the upper or lower genital tract and CA 125 levels.

Figure 2 shows the changes in the serum levels of CA 125 between acute phase and convalescent phase sera. Among those with elevated CA 125 levels initially, decreasing levels were seen in eight women and increasing levels in one. Rapid response to antimicrobial therapy occurred in all eight women with decreasing serum CA 125 levels.

Discussion

We have demonstrated a high prevalence of increased serum CA 125 levels in patients with

Table 1. Characteristics of the study population and serum CA 125 levels

	Serum CA 125 level (μg/l)	
	≥30 (positive) (n=10)	<30 (negative) (n=21)
Age (years)	31 (7)	23 (6)**
Parous women	7 (70%)	10 (48%)
Birth control method		
None	1 (10%)	4 (19%)
IUCD	6 (60%)	6 (29%)*
Hormonal	0 —	5 (24%)*
Other	3 (30%)	6 (29%)
Age at first coitus (years)	14 (7)	15 (5)
No of lifetime sex partners	2 (3)	3 (3)
History of past episode of PID	2 (20%)	8 (38%)
Duration of symptoms (days)	14 (10)	7 (8)*
Fever (≥38°C)	3 (30%)	2 (9%)
Clinical severity score Mean (SE)	11 (4)	10 (4)
Adnexal mass	6 (60%)	2 (10%)**
Bacterial vaginosis	5 (50%)	5 (29%)
Erythrocyte sedimentation rate	53 (25)	25 (15)**
C-reactive protein	72 (57)	43 (43)

Significance of difference between the two groups *$P<0{\cdot}05$, **$P<0{\cdot}01$.
Results are mean (SD) values and n (%) as appropriate.

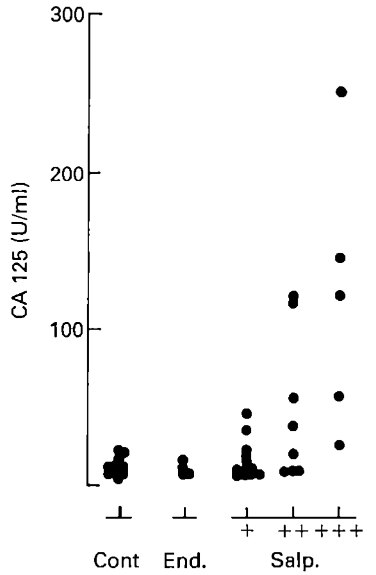

Fig. 1. Correlation of serum CA 125 levels with the severity of pelvic inflammatory disease. Cont , Control; End., endometritis only; Salp , salpingitis

laparoscopically or histopathologically proven acute PID. Approximately one third of patients with proven PID had elevated CA 125 levels; they were generally older, had longer duration of symptoms, had higher erythrocyte sedimentation rates, and more often adnexal mass on pelvic examination, and were more likely to be IUCD users and less likely to be oral contraceptive users. Elevated serum AFP, β_2-microglobulin, CA 15-3 and CEA levels were not detected among patients with PID (except one patient with slightly elevated CEA) further suggesting that PID specifically contributes to CA 125 elevation. By immunohistochemistry, using monoclonal antibody OC-125, CA 125 antigen has been demonstrated in the epithelium of endometrium and fallopian tubes and in the mesothelial cells of the peritoneum (Kabawat *et al.* 1983*a, b*). Oophoritis and salpingitis present in severe PID are generally associated with tissue damage, swelling, and necrosis likely to lead to rising serum levels of CA 125. Among patients with proven PID there was a strong correlation between high serum CA 125 levels and the severity of salpingitis, but the severity of endometritis did not correlate with CA 125 levels after adjusting for the severity of salpingitis. Severe salpingitis is almost invariably associated with severe oophoritis whereas mild salpingitis is generally associated with mild or absent oophoritis. Thus the presence of oophoritis may be more critical than the presence of salpingitis for elevation of serum CA 125. Our finding that 80% of patients with an adnexal mass had high CA 125 levels points to the same direction and supports the link between elevated CA 125 and oophoritis. Several studies have also shown that among patients with ovarian carcinoma, serum CA 125 levels correlate with the size of the tumour mass (Lambert 1987; Bast *et al.* 1983; Berek *et al.* 1986; Vergote *et al.* 1987). Malignant tumours, endometriosis, and oophoritis are all associated with disruption of the basement membrane. Such disruption probably leads the way to elevation of serum levels of CA 125.

Our results were almost identical to those of Halila *et al.* (1986) who found elevated CA 125 levels in 10 of 30 patients with suspected acute

Table 2. Serum CA 125 levels and isolation of specific micro-organisms from the upper or lower genital tract of patients with acute PID

	Serum CA 125 level (μg/l)	
	⩾30 (positive) (n=10) n (%)	<30 (negative) (n=21) n (%)
Upper genital tract		
C trachomatis	3 (30)	6 (29)
N. gonorrhoeae	0 —	2 (10)
M. hominis	2 (20)	3 (14)
Other specific bacteria	6 (60)	9 (43)
Upper or lower genital tract		
C trachomatis	4 (40)	10 (48)
N. gonorrhoeae	2 (20)	7 (33)
C. trachomatis or *N. gonorrhoeae* or both	6 (60)	13 (62)

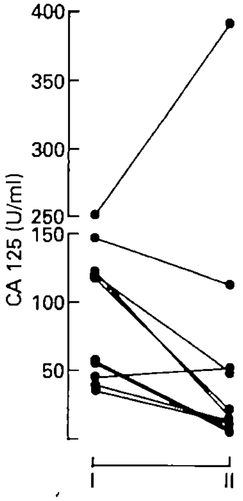

Fig. 2. Serum CA 125 levels in acute phase (I) and convalescent phase (II) sera from patients with acute pelvic inflammatory disease

PID. Although they did not confirm the diagnosis of PID by laparoscopy or endometrial biopsy, all their patients had fever and classic clinical findings of PID. Hence it was not surprising that one third of them had elevated CA 125 levels.

We were surprised that there was no correlation between chlamydial PID and high CA 125 levels. PID caused by *C. trachomatis* is usually associated with severe endometrial, adnexal and peritoneal inflammation, high ESR, and longer history of symptoms (Paavonen *et al.* 1987; Svensson *et al.* 1980). Perhaps the microbiological correlates of CA 125 should be more thoroughly studied in a larger study sample yielding higher numbers of patients with PID caused by specific micro-organisms.

We found remarkable changes in CA 125 levels between the acute phase and the convalescent phase sera. In fact, most patients responded well to the antimicrobial treatment. Good response to therapy is usually associated with resolution of tissue inflammation and disappearance of pelvic mass. Serial serum CA 125 determinations might be useful in monitoring response to therapy among patients with an inflammatory adnexal mass. Immunohistochemical studies are needed to learn more about the expression of CA 125 antigen in the inflammed tissue.

Our results are in agreement with previous studies demonstrating elevated CA 125 levels in many benign gynaecological conditions. These results confirm that CA 125 is less tumour specific than was initially believed. PID should be considered as a potential cause of false-positive CA 125 findings among young women with an adnexal mass. On the other hand, PID and oophoritis might predispose to ovarian carcinoma. Epidemiological studies are needed to show whether a past history of PID increases the risk of epithelial malignancy of the ovaries in later life.

Acknowledgments

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The pathophysiology of peri- and postmenopausal bone loss

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Summary. Changes in sex hormones and bone turnover were studied longitudinally in 31 women aged 47–54 years who were approaching the menopause. Every 6 weeks for 2–3 years, hormones and biochemical estimates of the bone turnover were determined and the bone mass was measured at two forearm sites by single photon absorptiometry. Spinal bone mass was measured every 6 months. The bone turnover was normal in women aged 47–54 years with regular menstruation, whereas the estimates of bone resorption were high in the women with irregular menstruation. In nine women, who reached the menopause during the study, bone resorption increased significantly, whereas bone formation showed only a small increase. When the results of the nine women were combined with those of 50 women, who had passed a natural menopause within the preceding 3·5 years, the bone resorption indices reached their peak within the first postmenopausal year, whereas bone formation increased until 1·5–2 years after the last menstrual cycle. At the ultradistal forearm site the rate of bone loss was maximal (5% per year) immediately after the menopause and subsequently declined, which suggests that trabecular bone is more sensitive than cortical bone to changes in bone turnover. Spinal bone loss was identical in late peri- and early postmenopausal women. We conclude that bone resorption starts to increase during the last perimenopausal years, with a beginning acceleration in bone loss, which then becomes sharp after the menopause. The changes are related to the decline in oestrogens, but other mechanisms may also play a role.

It is generally accepted that the rate of bone loss from all skeletal sites accelerates during the first postmenopausal years and subsequently declines (Geusens *et al.* 1986; Nilas & Christiansen 1988; Krølner & Pors Nielsen 1982). The postmenopausal bone loss is associated with a high turnover, i.e. both the resorption and the formation of bone are increased, but resorption is relatively greater and the outcome is a net loss of bone. The accelerated loss is a result of the declining ovarian function, and a similar loss is seen after oophorectomy (Richelson *et al.* 1984). Failing oestrogen production plays a central role in a mechanism not yet fully understood, but oestrogen receptors have recently been found in bone tissue (Eriksen *et al.* 1987).

Few women experience sudden cessation of their menstrual periods. Most pass through intervals with irregular cycles in an unpredicta-

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ble pattern. The time lapse between regular cycles and the cessation of menstrual periods—often called the perimenopausal transition—is 2 to 7 years in most women (Treloar *et al.* 1967). On a group basis, the oestrogen concentration declines during this time, but in the individual woman the hormones fluctuate and a postmenopausal hormone pattern may be followed by regular ovulatory cycles (Metcalf *et al.* 1981). Little is known about how these hormonal changes affect bone turnover. Some studies indicate that there is an incipient acceleration of trabecular bone loss in women approaching the menopause (Krølner & Pors Nielsen 1982; Johnston *et al.* 1985). With the techniques currently available for measuring bone mass, it is difficult to detect small temporal changes in the rates of bone loss. We have therefore undertaken a longitudinal study of changes in bone turnover during the perimenopausal transition by concentrating on biochemical markers of bone formation and bone resorption.

Subjects and methods

This study is part of a larger longitudinal study on the age-related changes in bone loss (Nilas & Christiansen 1988). The participants were 26 women aged 47–49 years and 13 women aged 51–54 years, who were recruited by questionnaires sent to 9836 women aged 45–54 years. All were healthy, none was receiving any kind of hormonal therapy, and all were menstruating regularly at the start of the study. Details of the inclusion criteria are given elsewhere (Nilas & Christiansen 1987). The study was planned to run for 2 years, and 31 (79%) completed this schedule. During this time only two women entered the menopause, defined here as at least 6 months without menstrual discharge, and therefore all participants were asked to continue the study.

The women visited the department every 6 weeks throughout the study, and at each visit oestrone, oestradiol, FSH, LH, phosphate, alkaline phosphatase and bone Gla-protein (BGP or osteocalcin) were determined in blood samples, and the creatinine corrected excretion of calcium (FU Ca/Cr) and hydroxyproline (FU Hpr/Cr) were measured in fasting urine. At each visit forearm bone mass was measured at two sites, and the lumbar spinal bone mass was measured every 6 months.

For comparison, we recruited 28 premenopausal women aged 29–45 years (mean 36 years) and 50 women aged 45–53 years (mean 50 years), who had passed a natural menopause 0·5 to 3·5 years earlier. The same schedule was followed except that the measurements were taken every 3 months; in the premenopausal women the hormone concentrations were measured twice at random during the cycle, and in the postmenopausal women plasma BGP was measured initially, and again at 3, 12 and 24 months. The 50 postmenopausal women were part of a subgroup of 58 women who completed the prospective study (Nilas & Christiansen 1988), but the remaining eight had one or two episodes of menstrual discharge during the study.

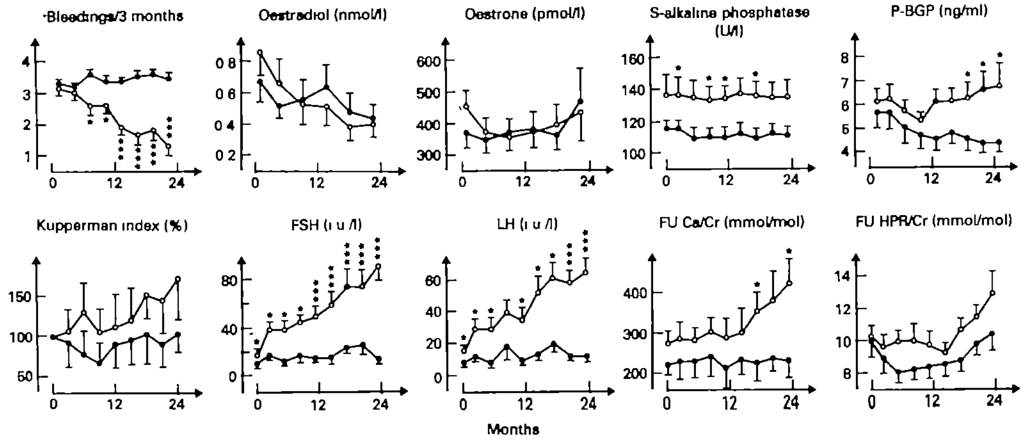

Fig. 1. Menstrual frequency, hormone levels, bone biochemistry, and forearm bone mass during the course of 2 years in 14 women with regular menstruation (●) and 17 women with irregular menstruation (○), given as mean (SE). *$P<0{\cdot}05$, **$P<0{\cdot}01$, ***$P<0{\cdot}001$, Student's *t*-test

The times of menstruation were entered on a calendar at each visit, but no attempt was made to obtain measurements on certain days of the menstrual cycle. Menopausal symptoms were scored according to Kupperman *et al.* (1953).

Measurements

Forearm bone mass was measured by single photon absorptiometry (SPA) and a multipath scan procedure at two adjacent forearm sites. Distal bone mineral content (BMC) has a reproducibility of 1·5% and a relative content of trabecular bone of about 50%. The corresponding figures for the proximal BMC are 1·0% and 10–15%. The spinal bone density (BMD) was measured by dual photon absorptiometry (DPA) on a Lunar Radiation Corporation Spine Scanner. During the study there were inter-source differences and, with some sources, drift of standard values as the source decayed. After the proper corrections had been made the long-term reproducibility was 3·7% (Nilas *et al.* 1988). Oestradiol and oestrone were measured in serum by radioimmunoassay (RIA) with antiserum and standards supplied by Malmö Isotop Laboratorium, Sweden, and Statens Serum Institut, Denmark, with interassay variations of 14% and 15%. LH and FSH were measured with antiserum from Diagnostic Products Corporation with interassay variations of 8% and 10%. Plasma Gla-protein was measured by RIA (Johansen *et al.* 1987). Antiserum was raised on rabbits immunized with purified intact calf BGP, and homogeneous calf BGP was used for tracer and standards. The inter- and intra-assay variations were 11% and 8%. Hydroxyproline was measured by spectrophotometry with an inter-assay variation of 12% (Pødenphant *et al.* 1984). Alkaline phosphatase, phosphate, calcium and creatinine were measured by routine techniques. These last four were measured the same day, the others from samples stored at −20°C until analysed. The BGP analyses were done in a series, the other analyses by degrees.

Calculations

The mean value of the biochemical measurements was calculated for each woman at different intervals, whereas the medians were used for the hormones (oestradiol, oestrone, FSH and LH). The mean, SD and SEM of the individual means/medians were then calculated within different groups. Differences between and within the groups were tested by the *t*-test for unpaired and paired data. The paired test was done on logarithmic values to ensure normal distribution. Changes in bone mass were calculated by linear regression analysis and are expressed in per cent per year.

Results

Fourteen women continued to menstruate monthly during the first 2 years of the study,

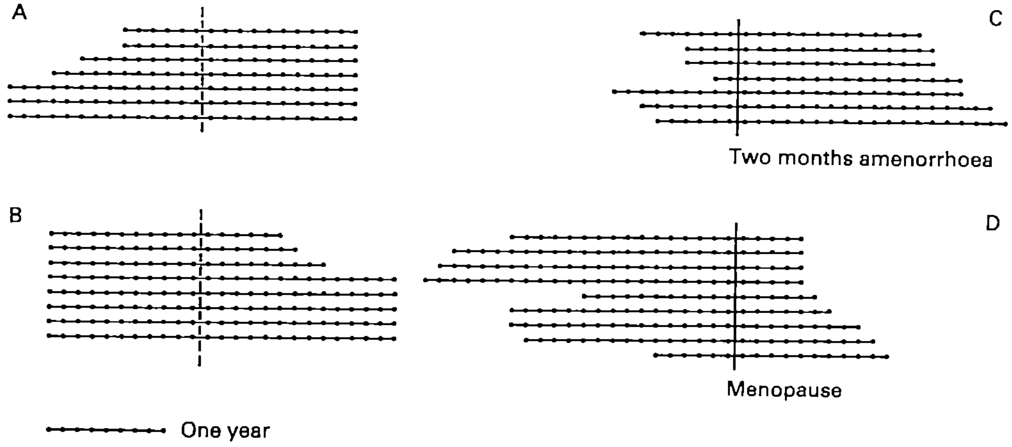

Fig. 2. Final study duration in the four perimenopausal groups. Each line represents one woman and each dot represents a visit where forearm bone mass, hormones and bone turnover were measured. The vertical lines indicate the time of division of the groups into two parts for the calculations in Table 1.

whereas the remaining 17 had intervals without menstruation at least on one occasion for more than 50 days. In the women with the regular cycles, the hormones and biochemical markers of bone turnover remained almost constant (Fig. 1). In the women who had intervals without menstruation, the oestradiol concentrations declined parallel to the declining menstrual frequency. There was an increase in gonadotrophin concentrations and indices of bone resorption (FU Ca/Cr and FU HPR/Cr) reaching postmenopausal values at the end of the 2-year period. At this time the oestradiol concentrations were within the lower part of the premenopausal range, and the indices of bone formation (BGP and alkaline phosphatase) were substantially lower than those seen after the menopause.

As only two women reached the menopause, the participants were asked to continue the study for another year, or until they reached the menopause. They were assigned to four groups in accordance with their menstrual pattern: group A included seven women with regular cycles of 21–35 days throughout the study; group B included eight women with slight deviations from the regular pattern; group C included seven women who had intervals without menstrual discharge for more than 2 months; and group D included nine women who reached the menopause. To calculate the changes within the groups, we divided the results of the biochemical and hormone determinations into two parts (Fig. 2). For groups A and B, this meant splitting the results in half, so that we had an equal number of observations in both parts, for groups C and D, the division was made at the time of the change in the menstrual pattern. These calculations are given in Table 1. The salient features are as follows. In group A the hormonal concentrations and bone turnover remained at the young premenopausal level. Group B showed a trend towards declining oestrogen and increasing gonadotrophin concentrations, but no definite changes in bone turnover. The hormonal changes were more pronounced in group C, and only small changes were found in the bone turnover despite elevated indices throughout the study. In group D, there were profound changes in all the variables and these are given on a time axis in Fig. 3. The mean bone loss for all the subgroups during the entire study is given in Table 2.

The nine women who reached the menopause were thereafter combined with the 50 postmenopausal women, who were ranked according to menopausal duration (Fig. 4). The semi-longitudinal data show an increase in the indices of bone resorption, which began before the menopause and peaked about 9 months after the last menstruation, and a decrease in FU Ca/Cr excretion during the years following the menopause. BGP increased slightly in the last premenopausal years and then abruptly reached stable levels about 1·5 years after the menopause. Alkaline phosphatases were constant up to the menopause, increased during the first 2 postmenopausal years, and remained unaltered throughout the rest of the study. The rate of bone loss from the two forearm sites increased significantly after the menopause and was maximal at the most distal site immediately after the menopause, thereafter declining (Fig. 4). At the proximal site the loss increased from 0·7% per year before the menopause to 2·0–3·0% per year after the menopause.

Discussion

Perimenopausal hormonal changes do not predict the postmenopausal pattern. On the contrary, they vary widely, both from woman to woman and from time to time in the same woman. One or two measurements of oestrogen and gonadotrophin concentration do not therefore necessarily reflect mean values in a woman. Comparison of the hormonal changes with changes in bone turnover is only relevant in groups of women, and we chose to divide them according to their menstrual pattern. Ovulation occurs in 93% of women with 21–35-day cycles (Metcalf 1979), and we found a fair relation between menstrual frequency and hormonal concentrations in women with irregular menstruations. The women were as unselected as possible and within the age span 45–54 years, chronological age has small effect on bone turnover compared with menopausal age (Nilas & Christiansen 1987).

Long-term changes in bone loss can be estimated by repeated measurements of bone mass. Although the SPA method has a reproducibility of 1%, it is not precise enough to measure changes occurring during the course of a few months, and here biochemical indices of bone turnover are preferred. We found that bone resorption increases during the perimenopausal transitional period, reaching postmenopausal

Table 1. Time-related changes in hormone and bone biochemistry in four groups of perimenopausal women (A, B, C and D). The pre- and postmenopausal values are also shown†

	Premenopausal ($n = 28$)	Group A ($n = 7$)		Group B ($n = 8$)		Group C ($n = 7$)		Group D ($n = 9$)		Postmenopausal (n=50)
		Part 1	Part 2	Part 1	Part 2	Part 1	Part 2	Part 1	Part 2	
Menstruations (no./3 months)	3·3 (0·3)	3·3 (0·2)	3·3 (0·2)	3·6 (0·2)	3·3 (0·5)	2·9 (0·4)	1·7** (0·8)	2·4 (0·3)	0***	0
Oestrone (pmol/l)	392 (135)	322 (69)	399 (122)	358 (106)	336 (110)	329 (145)	313 (87)	373 (82)	231*** (37)	249 (66)
Oestradiol (nmol/l)	0·54 (0·24)	0·49 (0·12)	0·46 (0·10)	0·56 (0·20)	0·32* (0·20)	0·47 (0·27)	0·27 (0·19)	0·51 (0·19)	0·07*** (0·04)	0·04 (0·04)
FSH (i.u./l)	10·6 (4·2)	11·7 (3·0)	11·0 (3·9)	14·7 (2·5)	31·6 (33·2)	25·1 (8·8)	48·4* (17·1)	48·7 (21·0)	132·7*** (26·7)	132·8 (33·2)
LH (i.u /l)	8·7 (4·8)	7·1 (2·0)	7·0 (1·5)	8·1 (3·9)	17·9 (16·2)	16·9 (6·1)	48·9** (22·0)	40·3 (14·9)	118·9*** (33·9)	66·1 (20·7)
Alkaline phosphatase (U/l)	124 (31)	119 (21)	118 (24)	111 (29)	112 (35)	152 (23)	150 (21)	118 (33)	132** (39)	173 (44)
BGP (ng/ml)	5·1 (1·9)	5·2 (2·4)	4·7 (1·7)	5·0 (1·8)	4·9 (1·5)	5·9 (1·6)	6·5 (1·2)	5·8 (2·0)	8·1** (3·7)	12·0 (3·7)
Phosphate (mmol/l)	1·19 (0·10)	1·09 (0·07)	1·06 (0·04)	1·20 (0·09)	1·19 (0·10)	1·10 (0·11)	1·18* (0·08)	1·11 (0·08)	1 19* (0·14)	1·21 (0·16)
FU Ca/Cr (mmol/mol)	165 (74)	229 (143)	219 (139)	225 (84)	244 (112)	262 (154)	326 (204)	332 (60)	466** (81)	379 (200)
FU HPR/Cr (mmol/mol)	9·4 (1·7)	9·5 (2·1)	10·7** (2·1)	7·7 (1·3)	10·3*** (1·5)	11·2 (4·1)	11·1 (3·0)	9·9 (2·1)	13·8*** (3·2)	14·1 (3·4) * ** ***

†For each group of perimenopausal women the results were divided into two parts (as described in text) and are shown as mean (SD) values. Differences within each group are tested by t-test for paired data (*$P<0·05$, **$P<0·01$, ***$P<0·001$)

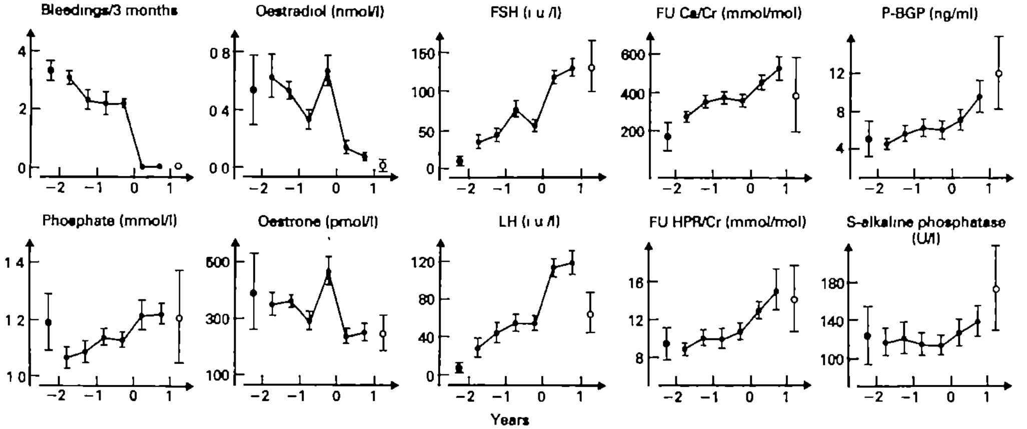

Fig. 3. Time-related changes in menstrual frequency, hormones and bone turnover in nine women (group D), who reached the menopause. The *X* axis is given in years before and after the menopause and the values on the *Y* axis are given as mean (SE). The mean (SD) values for the premenopausal (●) and postmenopausal (○) control groups are given for comparison.

levels when the menstrual frequency had declined to 1–2 per 3 months, but was maximal 9 months after the menopause. Others have found that calcium excretion continues to decline, approaching premenopausal values about 20 years later (Nordin & Polley 1987). The perimenopausal increase in bone resorption was followed by a small increase in BGP, whereas alkaline phosphatases remained unchanged, indicating that these substances reflect different steps in the formation of bone. We found a continuing increase in bone formation for the first 1–2 postmenopausal years whereafter stable values were reached. Both during the perimenopausal years and the first postmenopausal period, the measured rates of bone loss corresponded to the differences between bone formation and bone resorption.

Our results thus indicate that there is a gradual increase of bone loss during the perimenopausal years but that the loss accelerates sharply immediately after the menopause. In contrast, Slemenda *et al.* (1987) have found almost similar rates of forearm bone loss in late perimenopausal and early postmenopausal women. Most of their late perimenopausal women passed the menopause and it is possible that the bone loss in these women occurred in different phases at different rates. The relation between the bone turnover and ovarian function found in the present study indicates that women with a long perimenopausal transition, long intervals without menstruation, and low oestrogen concentrations may lose a substantial amount of bone and have a high bone turnover when entering the menopause. In the nine women who became postmenopausal during our study the perimenopausal transition was short and the changes in bone turnover occurred rather suddenly.

Bone changes during the perimenopausal and the first postmenopausal years are greater at the

Table 2. Rates of bone loss (per cent per year) from two forearm sites and the spine during the entire study in pre-, peri- and postmenopausal women

		Bone mineral content		
		Proximal	Distal	Spinal bone density
Premenopausal	($n = 28$)	−0·14 (0·65)	−0·56 (0·95)	−0·15 (2·29)
Groups A and B	($n = 15$)	−0·43 (0·35)	−0 57 (0·50)	0·04 (2·67)
Group C	($n = 7$)	−0·57 (0·46)	−0·85 (0·60)	−0·52 (1 34)
Group D	($n = 9$)	−0·90 (0·68)	−1·13 (1·04)	−2·52 (1·90)
Postmenopausal	($n = 50$)	−2·11 (1·44)	−2·86 (1·98)	−2·36 (4·24)

Values are given as mean (SD).

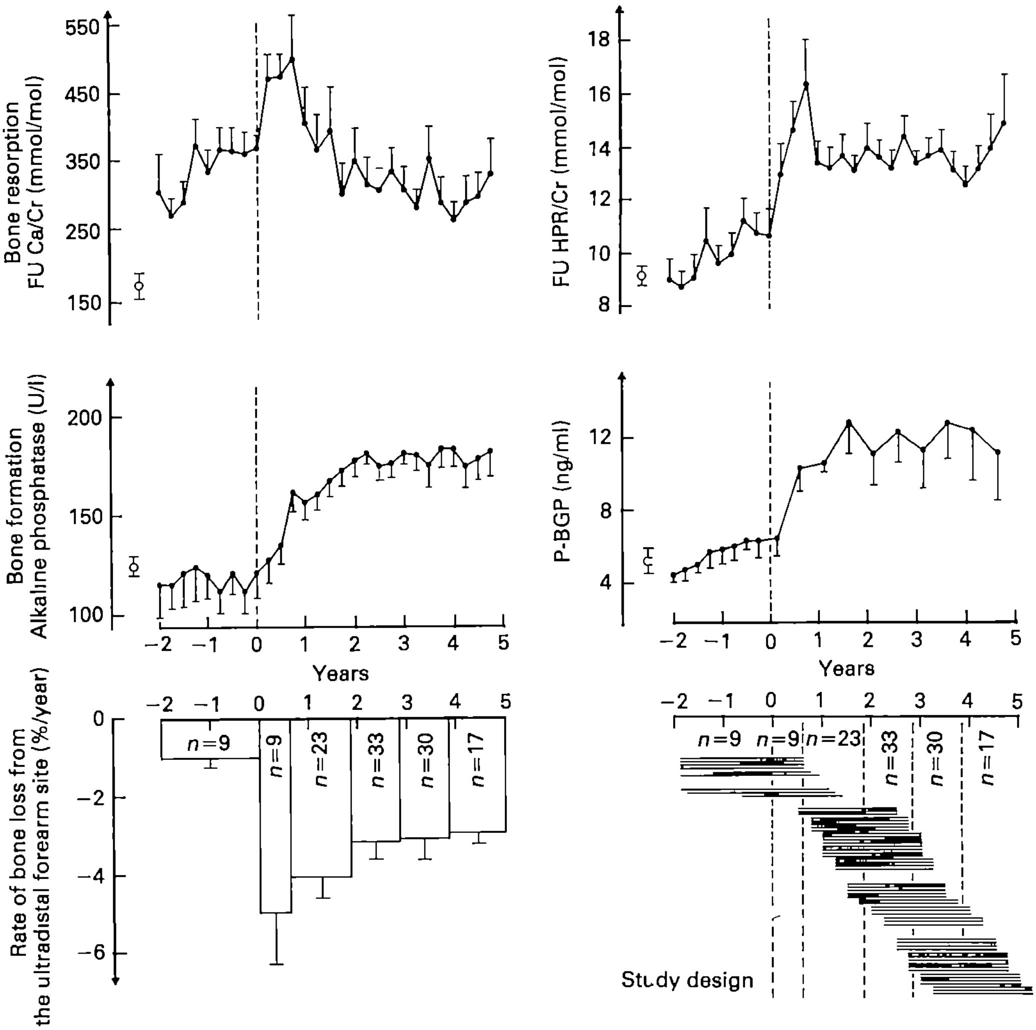

Fig. 4. Bone biochemistry and rate of bone loss together with the study design, for the combined group of nine women reaching the menopause (group D) and 50 women who had already passed a natural menopause. The biochemical values are given as mean (± 1SE) with the premenopausal normal range (mean ± 1SE) on the left. The individual rates of bone loss were calculated in 2-year periods before the menopause, 6 months immediately after, and then in 1-year periods. In the diagram of the study design each line represents one woman. The vertical lines indicate the intervals at which the mean rate of bone loss was calculated.

distal forearm site than at the more proximal site, which suggests that trabecular bone is more sensitive to changes in bone turnover than is cortical bone. We found no acceleration of spinal bone loss during the first perimenopausal years, but equally high rates of loss in late perimenopausal and early postmenopausal women. We have observed a spinal bone loss of 4–5%/year within the first 3 postmenopausal years (Nilas & Christiansen 1988). With a reproducibility of spinal measurements of 4% and the relatively few measurements, we cannot in the present study show whether or not the spinal loss accelerates immediately after the menopause.

The close relation between changes in bone turnover and oestrogen concentration supports the theory that the rapid postmenopausal bone loss is caused by a lack of inhibition of bone resorption mediated through oestrogens. Both in earlier cross-sectional data (Nilas & Christiansen 1987) and in the present longitudinal study, we have, however, found an elevated FU Ca/Cr ratio in early perimenopausal women who had oestrogen concentrations within the premenopausal range, but raised gonadotrophin concentrations. Oestrogens fluctuate during a normal menstrual cycle, apparently without a similar fluctuation in either bone turnover or calcium-regulating hormones (Baran *et al.* 1980; Tjellesen *et al.* 1983). The dissociation of the normal feedback regulation between oestrogens and gonadotrophins during the early perimenopause is well known but the cause is debatable (Sherman & Korenman 1975; Reyes *et al.* 1977). Our data and those of others (Slemenda *et al.* 1987) indicate that some of the postmenopausal loss of bone is mediated by mechanisms other than oestrogens. Reduced progesterone production may have an effect, but it is tempting to seek a common explanation for the early increase in bone resorption and gonadotrophin concentrations.

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Doppler time velocity waveform studies of the uterine artery and uterus

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Summary. This study describes a reliable and reproducible method of obtaining Doppler frequency shift waveforms from the uterine artery based on observations in 26 non-pregnant women. The waveforms were detected easily but direct display of the vessel was inconsistent. The values of the pulsatility index calculated from the waveforms had a mean of 3·25 (SD 0·83). The standard error of the mean was 0·16 and based on this, the 95% reference range was 1·21 to 5·29. The stage of the menstrual cycle did not affect the pulsatility index nor was there any significant difference between subjects who were nulliparous and those who had had previous pregnancies. These results show that Doppler ultrasound can be applied to the non-pregnant uterus and the data presented may be used as a baseline for the study of uterine pathology.

Doppler ultrasound utilizes the changes in frequency that occur when sound is scattered from objects moving relative to the source of the sound. It may be applied to the investigation of blood flow velocities where sound scattering occurs from red blood cells in the circulation (Gosling 1976; Gill 1979; Jonnart 1981). Its advantages over other methods such as arteriography and digital subtraction angiography are that it is non-invasive, painless and has no associated morbidity or mortality. Thus, it is more suitable for serial studies. The ultrasound may be produced either continuously or in pulses with a very rapid repetition rate. In both cases frequency shifted signals are returned from the entire length of the beam. The usefulness of continuous wave Doppler ultrasound is limited as the frequency shifted signals returned cannot be separated in order to examine a particular area. Thus, it is mainly used in superficial vascular analysis and obstetrics where the anatomical position of the vessel of interest is sufficiently isolated from moving neighbouring structures that there is little or no interference. The introduction of combined real-time and pulsed Doppler ultrasound (duplex) systems has made it possible to see and investigate haemodynamic aspects of deep and complicated vasculature. A variable time-gating mechanism which can preselect the desired returned frequency changes between pulses allows a particular vessel to be sampled. This has enabled the vasculature of the pelvis to be investigated, and the potential for studying pathology in this region, especially tumours, is now great.

The study of the uterine artery and uterus using this method has been mainly confined to pregnancy and fetal medicine (Campbell *et al.* 1983; Cohen-Overbeek *et al.* 1985) and little

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information is available on this vessel in other states. In this study we have described and applied Doppler ultrasound scanning techniques to the normal uterine arteries and myometrium.

Subjects and methods

The study included 26 volunteer women whose ages ranged between 19 and 52 years (mean 27·7, SD 8·0) who were scanned on a single occasion. Each had a brief history taken, noting the first day of their last menstrual period and the number and outcome of any previous pregnancies. Only those who had regular menstrual cycles, who were not taking oral contraceptive agents or were under treatment for infertility and who had no previous history of any pelvic disorders were entered into the study.

Scanning technique

The subjects were required to have a full bladder to allow good ultrasonic access to the pelvis and each underwent a real-time scan to exclude any unknown abnormalities. The uterine volume was calculated using the prolate ellipsoid formula where:

$$\text{Volume} = L \times A\text{-}P \times W \times 0{\cdot}523\ \text{cm}^3$$

(L=length, A-P=maximum antero-posterior diameter, and W=maximum width).

The Doppler investigations used a Diasonics DRF 400 duplex scanner with a 3·5 MHz mechanical sector probe. The returned changes in frequency were displayed on a monitor using an on-line spectrum analyser with a high pass filter set at 150 Hz. The resulting spectra were recorded on to photographic paper when three consecutive waveforms with little or no interference were obtained.

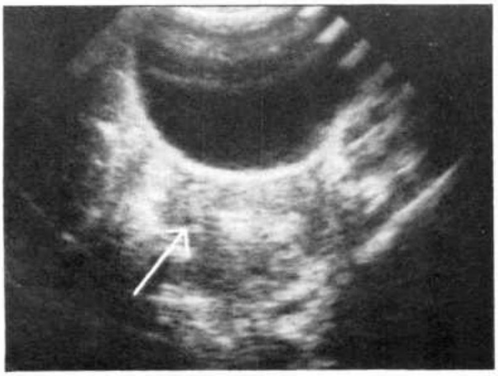

Fig. 1. Transverse section of the uterus at the level of the supravaginal portion of the cervix. The uterine artery can be demonstrated as a small transonic area approximately 2 to 3 mm in diameter (arrow).

The frequency shifted spectra from the uterine arteries could be easily detected by scanning transversely at a level just above and adjacent to the supravaginal portion of the cervix. Occasionally, the uterine artery could be seen as a small pulsating transonic area measuring approximately 2 to 3 mm in diameter (Fig. 1), but the uterine vein had similar appearances and the two could not be differentiated purely on sonographic morphology. Care was taken not to scan above this level as signals from the anastomosis of the uterine artery with the ovarian artery may be included in the returned spectra. When the waveform was detected the procedure was repeated on the opposite side. In the anteverted uterus, flow in the uterine arteries should be towards the probe resulting in a positive frequency change. If the uterus is retroverted then flow may be in the opposite direction resulting in a negative frequency change. In this situation the position of the area under investigation must be carefully noted as flow in the internal iliac arteries and vaginal branch of the uterine artery can also be away from the probe.

The myometrium and endometrium were then scanned and sampled at multiple points in several longitudinal and transverse sections.

Signal analysis

Blood velocity can be calculated from the frequency spectra generated providing the angle at which the insonating Doppler beam subtends to the vessel being sampled is known. The Doppler equation is:

$$v = \frac{df\,c}{2f\cos\theta}$$

where v is the velocity of the scattering surface, df is the change in frequency, c is the speed of ultrasound in tissue (1540 m/s), f is the insonating ultrasonic frequency, and θ is the angle at which the ultrasound beam subtends to the vessel of interest. In the case of the uterine arteries it is not possible to measure the angle θ because of their small diameter and tortuous course. Therefore, the pulsatility index (PI) (Gosling 1976), which is independent of the angle of insonation, was chosen to analyse the waveforms. This is defined as:

$$\mathrm{PI}=\frac{A-B}{\text{mean}}$$

where, taking into consideration the waveform envelope over one cardiac cycle, A is the maximum change in frequency during systole, B is the minimum frequency change in diastole, and mean is the average frequency change (Fig. 2). The PI reflects the impedance to blood flow in the vessel distal to the point of sampling. Providing proximal conditions of blood flow remain constant, an increase in distal impedance will result in an increase in the PI and, correspondingly, a decrease in distal impedance will result in a decrease in the PI.

Reproducibility

Isolation of the uterine artery waveform. The uterine artery waveform was detected and recorded in 10 subjects. The probe was then removed from the abdomen and the waveform was relocated after a time interval of at least 5 min and recorded in the normal way. The mean PI of the results was 3·52 (SD 0·31) and the coefficient of variation was 8·8%.

Calculation of the PI. The PI was calculated in the normal way in 10 subjects and then recalculated from the same hard copy of the waveforms with an interval of at least 48 h. The mean PI of the results was 3·04 (SD 0·04) and the coefficient of variation was 1·3%.

Thus, it can be concluded that the methods of localizing the uterine artery and analysing the returned frequency spectra are reproducible.

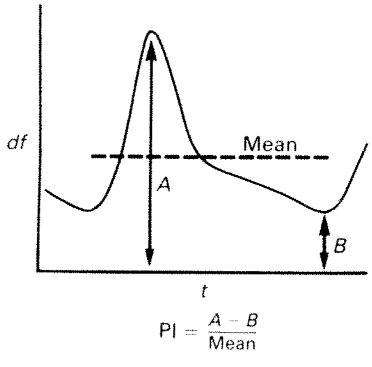

Fig. 2. The calculation of the pulsatility index.

Results

Waveform shape

The waveform generated by the uterine artery in the normal pelvis is one that is a product of a moderately high impedance to flow (Fig. 3). It shows a rapid increase of Doppler shift frequencies followed by an abrupt fall during systole giving rise to a sharp peak. There is usually a small diastolic component ending in few or no frequency changes. The frequency spectra show few characteristics of laminar flow, which is not surprising considering the tortuosity of the vessel.

Pulsatility index

Uterine arteries. The range of PI calculated in the 26 subjects was 1·67–5·23 (mean 3·25, SD 0·83) (Fig. 4). Where both the left and right uterine arteries were measured in the same subject, only one result was used in the analysis which was then repeated with the other result. The means and standard deviations were identical. The data conformed to a normal distribution (skew 0·187, $P>0·5$). In the first 10 subjects both the left and right uterine arteries were measured to establish whether there was a differential impedance to flow (Fig. 5). The mean PI was 3·01 (SD 0·65) in the left uterine artery and 3·03 (SD 0·71) in the right uterine artery (paired t-test, $P>0·8$).

Stage of menstrual cycle. The subjects were assumed to be ovulating as they all had regular menstrual cycles, had no history of previous gynaecological problems and were not taking any hormone preparations. The subjects were grouped as to whether they were before or after ovulation. This was calculated by assuming that the time from ovulation to the ensuing menstrual period is constant at 14 days. The pre-ovulatory group had a mean PI of 3·23 (SD 1·03) and the post-ovulatory group had a mean PI of 3·28 (SD 0·71) (unpaired t-test, $P>0·8$).

Previous pregnancies. Twelve subjects with no previous pregnancies had a mean PI of 3·38 (SD 0·60). Fourteen subjects with one or more previous pregnancies had a mean PI of 3·17 (SD 0·98). Of the group with previous pregnan-

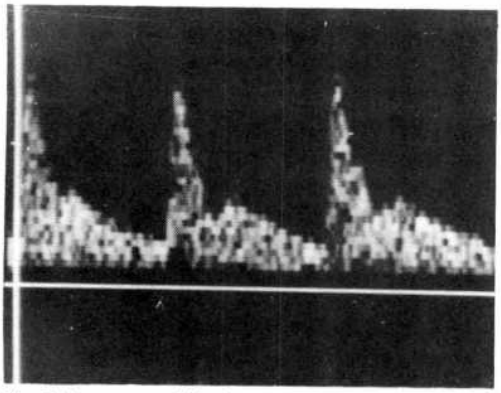

Fig. 3. Frequency shifted spectra of the uterine artery.

cies eight had term deliveries and six had terminations of pregnancy only. Four of the subjects with term deliveries had had other pregnancies, three with miscarriages and two with terminations of pregnancy.

There was no significant difference in PI between subjects who had no previous pregnancies and those who had (unpaired *t*-test, $P>0\cdot5$), whether they had a term delivery ($P>0\cdot9$) or a pregnancy which did not reach term ($P>0\cdot1$). Nor was there any significant difference in PI between those who had a term delivery and those whose pregnancies did not reach term ($P>0\cdot2$).

Age. The mean age of the study sample was 27·7 years (SD 8·0). There was no correlation between the PI of the uterine arteries and age of the subjects ($r=-0\cdot09$, $P>0\cdot5$).

Uterine volume. This ranged from 30 to 135 cm^3 with a mean of 84·5 (SD 28) cm^3. There was no correlation between the PI and volume ($r=-0\cdot11$, $P>0\cdot5$).

Myometrial signals

Some low intensity venous signals could be detected at the lateral margins of the myometrium and probably arose from the uterine veins, but no Doppler frequencies were returned from within the myometrial stroma or endometrium.

Discussion

Pulsed Doppler ultrasound is a relatively new technique giving information that relates to the physiological state of the circulation (Gosling 1976; Skidmore & Woodcock 1980). To gain an understanding of the information gathered in this way, it must be considered in association with the anatomical structure of the organ under investigation. The uterus has an extensive microvascular network (Schlegal 1946; Farrer-Brown *et al.* 1970). These many small vessels would give rise in the non-pregnant state to the high impedance to flow which is demonstrated by the uterine artery Doppler frequency changes. Taylor *et al.* (1985) stated that the uterine artery waveform was a result of a high impedance to flow but did not attempt to analyse the frequency spectra quantitatively. However, they did calculate a series of PI values for the internal iliac arteries where they found the mean PI to be 2·81 (SD 0·93) (approximate range 1·5–5·3). The PI values of the uterine artery found in the present study correspond closely with these data. This is not surprising as anatomically the uterine artery is the main branch of the internal iliac artery in women of reproductive age. By considering the 95% confidence limits of the mean of our results, the extremes of PI of the 95% reference range can be set at 1·29 to 5·20.

There was no significant difference in the impedance to blood flow between the left and right uterine arteries, which would indicate that blood is equally distributed to both sides of the uterus. Other evidence also supports this. Injection studies performed on specimens resected at operation or at autopsy have shown that dye penetrates uniformly through the endometrium (Schlegal 1946).

The increase in blood flow to the uterus in response to oestrogens is well documented (Williams 1948; Reynolds 1949; Greiss & Marston 1965; Salvatore 1968; Greiss & Anderson 1970). In general, it is greatest when oestrogen

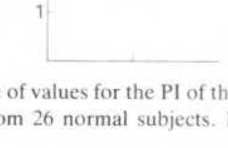

Fig. 4. Range of values for the PI of the uterine artery calculated from 26 normal subjects. Mean 3·25, SD 0·83.

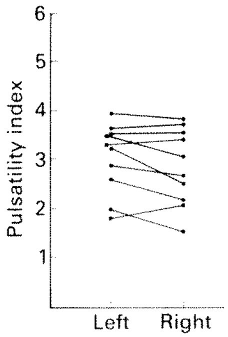

Fig. 5. Values of the left (mean 3·01, SD 0·65) and right (mean 3·03, SD 0·71) uterine arteries in 10 subjects.

levels are high (Gilman 1941; Kalman 1958; Dickson *et al.* 1969) which is during the week preceding ovulation and during the secretory phase of the endometrium. Thus, we may have expected some difference in the frequency spectra before and after ovulation but none was found. We did not assess the uterine arteries serially throughout the menstrual cycle which would better detect differences in PI. Doppler analysis of the ovarian arteries (Taylor *et al.* 1985) has revealed that there is a lower impedance pattern in the artery supplying the ovary containing the dominant follicle. Our results do not indicate that this relation occurs in the uterine arteries. It is possible that the needs of the early conceptus are adequately catered for by the blood-filled decidual sinuses and that the vascular state of the uterus at the time of conception is not of great importance. Obviously, the haemodynamic changes of the uterine circulation during the menstrual cycle and early pregnancy using Doppler ultrasound need further study.

No Doppler signals were detected from either the myometrium or endometrium and it is probable that the impedance produced by the uterine microvasculature results in a very low blood velocity which is not detectable by Doppler ultrasound. Additionally, the arterial supply to the endometrium is relatively sparse when compared with that to the myometrium (Farrer-Brown *et al.* 1970). This would further reduce the intensity of any frequency changes produced by decreasing the density of red blood cells which act as the scattering surfaces to the ultrasound.

The effects of pregnancy on the uterine circulation are well documented (Browne & Veall 1953; Assali *et al.* 1960), and Doppler frequency shift waveforms indicate a low impedance to flow (Campbell *et al.* 1983; Griffin *et al.* 1983; Cohen-Overbeek *et al.* 1985; Trudinger *et al.* 1985; Trudinger & Cook 1985). The waveforms we detected were very different from those found in the pregnant state. However, the substantial impedance changes in pregnancy do not appear to be long lasting, and subjects with previous pregnancies, whether they reached term or not, did not have a lower PI than those who had never been pregnant. Abnormal arterio-venous communications in the uterus are rare and are usually associated with gestational trophoblastic tumours where the invasive properties of trophoblast are exaggerated (Frencken & Landman 1965; Brewis & Bagshawe 1968). Their diagnosis is usually made after presentation of the patient who subsequently is investigated by pelvic angiography. The use of Doppler ultrasound in these cases can demonstrate large low impedance channels within the uterus (Long *et al.* 1987). This will save the need for an invasive and potentially hazardous procedure in otherwise well young women.

This study demonstrates the potential for Doppler ultrasound to investigate pelvic vascular physiology. The applications of this technique are rapidly widening and may soon be applied to the monitoring of patients being treated for tumours or infertility. However, the important field of assessing the normal haemodynamic state of the uterus as an aid to understanding pelvic pathology has been rather neglected. It is hoped that the results presented in this paper will act as a comparison to other studies using Doppler ultrasound in the pelvis to delineate normal and abnormal uterine blood flow.

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Phaeochromocytoma in pregnancy. Five cases and a review of the literature

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Summary. We report five patients with phaeochromocytoma associated with pregnancy and review the 42 other cases reported in the literature from 1980 to 1987. The overall maternal mortality was 17% and the fetal loss 26%; antenatal diagnosis of phaeochromocytoma reduced the maternal mortality to zero and the fetal loss to 15%, but was made in only 53% of the patients. Although phaeochromocytoma is rare, a high index of clinical suspicion must be maintained and all those at risk investigated if earlier diagnosis and improved outcome are to be achieved. Once the diagnosis is confirmed, alpha-blockade is essential and beta-blockade may be required. CT scan or magnetic resonance imaging may be used to localize the tumour during the antenatal period. In the first and second trimesters, tumour resection has a good fetal outcome; in later pregnancy, delivery by elective caesarean section followed by tumour resection is recommended.

Phaeochromocytoma in association with pregnancy is rare, but important because of the potentially disastrous consequences for both mother and fetus. Phaeochromocytoma in association with pregnancy has occurred in five patients during the last 10 years in the Northern Ireland population of approximately 1·5 million, with 27 000 livebirths per year (Registrar General 1985), suggesting that these tumours may be present more often in pregnancy than is indicated by the 180 or so cases reported to date. We report here our experience of the management of these five patients and review the recent literature.

Patient 1

A 39-year-old woman presented in September 1977 with a blood pressure of 180/90 mmHg at 10 weeks gestation in her third pregnancy. One year previously she had been started on treatment with propranolol because of hypertension (160/100 mmHg) and episodes of heaviness in the chest. A chest radiograph and electrocardiogram at that time were normal. Her treatment was changed from propranolol to gradually increasing doses of alpha-methyldopa. Her blood pressure remained stable until 28 weeks gestation when it was 210/130 mmHg and she had developed proteinuria. After admission she developed generalized oedema, frontal headache and visual symptoms. Caesarean section

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under general anaesthesia at 28 weeks and 5 days gestation resulted in the birth of a 1160-g male infant who initially developed severe respiratory distress but subsequently made good progress.

Postoperatively she became increasingly hypertensive (blood pressure 220/145 mmHg) with agitation, impaired consciousness, laboured breathing, tachycardia, peripheral vasoconstriction and oliguria. Central venous pressure was 25 cm H_2O. Oxygen was administered and frusemide, 40 mg, given intravenously with no immediate response. Approximately 1 h later the central venous pressure fell suddenly to 12 cm H_2O with improved peripheral circulation and urinary output, and the blood pressure fell to 160/120 mmHg. Propranolol, 1 mg intravenously, was given with further reduction of her blood pressure to 120/80 mmHg.

Subsequent investigation showed marked elevation of urinary catecholamine excretion (several 24-h urinary total catecholamine specimens collected had values ranging from 6·6 to 211 μmol/24 h, normal range <0·65 μmol/24 h) confirming the diagnosis of phaeochromocytoma. CT scan of the abdomen and a femoral aortogram performed after preliminary alpha-blockade with phenoxybenzamine showed a large vascular right-sided pre-renal mass. Vena caval sampling for plasma noradrenaline showed an isolated peak opposite the right adrenal vein confirming this finding. At laparotomy, a 130-g right extra-adrenal phaeochromocytoma was excised. Both adrenal glands were normal.

Postoperatively, catecholamine levels returned to normal. Five years later the patient developed a metastasis in the skull and massive recurrence of tumour along the lower aorta. All detectable tumour was resected surgically. Urinary noradrenaline levels remained raised although she was asymptomatic and normotensive. Subsequently she developed an abdominal mass and lumbar spine metastases. Treatment with therapeutic doses of meta-iodobenzylguanidine was not helpful. More recently, combination chemotherapy of cyclophosphamide, vincristine and dacarbazine (Keiser *et al.* 1985) has led to good symptomatic improvement and shrinkage of the abdominal mass. She continues on this regimen.

Patient 2

This 37-year-old primigravida with multiple neurofibromata was normotensive before pregnancy. She attended an antenatal clinic regularly. The highest recorded blood pressure was 136/80 mmHg, and 4 days before presentation was 100/40 mmHg. On 28 June 1980, at 37 weeks gestation, she suddenly complained of nausea, chest pain and intense headache. She had a fit during which she coughed up blood. On admission to the local hospital she was breathless, cyanosed, semi-comatose and shocked (respiratory rate 50/min; blood pressure 90/? mmHg; pulse 180 beats/min). Massive pulmonary embolism was suspected and she was treated with oxygen and heparin. However, a chest radiograph suggested aspiration pneumonitis. Steroids and antibiotic cover with ampicillin, flucloxacillin and gentamicin were given. There was some improvement (blood pressure 120/100 mmHg; pulse rate 160 beats/min) and she was able to give a brief history before suffering further chest pain and collapse. Despite immediate ventilation with 100% oxygen she remained comatose and peripherally cyanosed and blood gases could not be maintained. At this stage her blood pressure was 220/130 mmHg and the fetal heart could not be heard. A further chest radiograph showed typical signs of progressing Mendelson's syndrome. She was transferred to the regional respiratory intensive care unit. Phenoxybenzamine was given and a dopamine infusion was started but her condition deteriorated and cardiac arrest occurred 19 h after the initial presentation.

At autopsy a 4 cm right adrenal phaeochromocytoma was found. There were pleural and pericardial effusions and cerebral oedema but no evidence of pulmonary infection, infarction, or emboli. The unborn male fetus weighed 2500 g. The 500-g placenta had several areas of retroplacental haemorrhage.

Patient 3

A 24-year-old primigravida presented in 1982 with progressive hypertension. At 11 weeks amenorrhoea her blood pressure was 120/80 mmHg, at 16 weeks 150/92 mmHg, and at 18 weeks 180/110 mmHg. After admission she was observed to have episodic hypertension (blood pressure up to 180/110 mmHg) with tachycardia. Although previously asymptomatic, she complained of constant perspiration and anxiety. Urinary catecholamines were markedly elevated (total catecholamines 3·92 μmol/24 h, normal range <0·65 μmol/24 h; noradrenaline 561 μg/

24 h, normal range 14–80 μg/24 h; adrenaline 199 μg/24 h, normal range 0·5–20 μg/24 h. Ultrasound and digital angiography, performed after preliminary alpha-blockade with phenoxybenzamine, showed a tumour in the right adrenal region. Venous sampling for adrenaline showed levels of 88 nmol/l in the right adrenal vein compared with levels of 8 nmol/l in the low inferior vena cava. After adequate alpha blockade had been established, a 32-g right adrenal phaeochromocytoma was removed at 23 weeks gestation. At 32 weeks gestation she was readmitted with hypertension (blood pressure 135/95 mmHg). Her blood pressure remained at this level without proteinuria until labour was induced at 38 weeks gestation, resulting in the normal delivery of a healthy 2920-g female infant. Since then the patient has remained well with mild hypertension (blood pressure up to 140/90 mmHg), normal catecholamine levels and no evidence of recurrent tumour. She had an uncomplicated second pregnancy in 1984.

Patient 4

This 39-year-old woman presented in 1984 in her fourth pregnancy at 7 weeks amenorrhoea with a blood pressure of 200/120 mmHg. In the past 5 years she had had one normal pregnancy and two miscarriages. All previous blood pressure recordings had been normal. She had no symptoms apart from a long history of recurrent frontal headache. She was admitted for investigation. Urine noradrenaline levels were markedly elevated (2315–4332 nmol/24 h, normal range 50–560 nmol/24 h). Treatment with labetalol, 200 mg three times daily, was started. Ultrasound showed a mainly cystic 5-cm right adrenal mass. CT scan showed a 6-cm cystic tumour of the right adrenal gland and enlargement of the lower pole of the left adrenal gland with central necrosis. She had a diffuse goitre with a palpable nodule. Serum free thyroxine was normal.

Bilateral adrenalectomy under alpha- and beta-blockade with phenoxybenzamine and propranolol was performed at 16 weeks gestation. A 5-cm cystic phaeochromocytoma replaced the right adrenal gland. A 2-cm phaeochromocytoma was present in the left adrenal gland. It was decided to defer operation on the thyroid until after delivery unless it changed markedly in size.

The remainder of the pregnancy was uncomplicated. Replacement therapy with hydroxycortisone and fludrocortisone was given. No changes occurred in the thyroid gland. Spontaneous labour at 37½ weeks resulted in the birth of a healthy 3180-g male infant. Subsequent thyroidectomy showed a multinodular colloid goitre with no evidence of medullary carcinoma of the thyroid. She remains well with normal blood pressure and catecholamine levels.

Patient 5

This 28-year-old woman developed hypertension and proteinuria near term in her first pregnancy in 1986. Labour was induced. She was hypertensive, blood pressure 160/110 mmHg during labour, and was treated with pethidine, hydralazine and diazepam. Caesarean section was performed because of fetal bradycardia and a live 3770-g male infant was born. After the delivery she became oliguric and relatively hypotensive for a short time. Two days later she coughed up some blood. Lung scan was normal, but electrocardiograph showed evidence of myocardial infarction and cardiac enzymes were elevated. She remained normotensive and made a rapid recovery. There was no relevant family history. Subsequent investigations including fasting serum lipids, glucose tolerance test, treadmill test, thallium scan and blood pressure at follow-up outpatient visits were normal.

The patient was normotensive throughout the antenatal period in her second pregnancy but in November 1987 she experienced the sudden onset of hypertension during labour with spikes of blood pressure to 220/120 mmHg. She was treated with pethidine and diazepam. Repeat caesarean section was performed because of failure to progress in labour. During induction of anaesthesia her blood pressure reached 230/135 mmHg, her pulse rate slowed to 50 beats/min with a bigeminal rhythm, and there was fetal bradycardia. She was treated with phentolamine by intravenous infusion and a healthy 3000-g male infant was born. The blood pressure settled to 120/80 mmHg. Over the next 48 h there were minor rises in blood pressure—one of these was thought to have been provoked by an injection of pethidine. Subsequent investigation showed elevated urinary noradrenaline of 1512–2413 nmol/24 h (normal range 50–560 nmol/24 h) and dopamine of 2984–6335 nmol/24 h (normal range 310–3900 nmol/24 h) although adrenaline levels of 16–23 nmol/24 h fell within the normal range (5–120 nmol/24 h). A CT scan showed a 5 × 3·5 cm mass below the left renal pedicle. This was removed under alpha-blockade with phenoxybenzamine and beta-blockade with propranolol, and the diagnosis of phaeochromocytoma was confirmed. Postoperatively she is normotensive with normal urinary catecholamine levels.

Discussion

Phaeochromocytoma produces similar symptoms and signs in both pregnant and non-pregnant patients, but the diagnosis may be overlooked in pregnancy because of the rarity of the association and because the clinical picture often mimics that of pre-eclampsia (Badui *et al.* 1982). An unrecognized phaeochromocytoma is particularly dangerous, as potentially fatal hypertensive crises may be precipitated by anaesthesia, vaginal delivery, the mechanical effects of the gravid uterus, uterine contractions, and even vigorous fetal movements. The maternal mortality is high. In 162 pregnancies associated with phaeochromocytoma in 139 patients, the maternal mortality before 1969 was 48%, although it fell to 26% in the period 1969–1979 (Schenker & Granat 1982) and continues to fall (17% in the period 1980–1987 and including our five patients; see Table 1), reflecting improvements in management. When the diagnosis was made antepartum, the maternal mortality fell to 11% (Schenker & Granat 1982) and more recently (Table 1) to zero.

Fetal growth retardation may occur secondary to reduced uteroplacental perfusion, and fetal hypoxia and death may occur during acute hypertensive crises, maternal collapse or death. Antepartum diagnosis and alpha-blockade reduce the fetal mortality (Burgess 1979). After the introduction of adrenergic blocking agents, the fetal loss decreased from 50% to 30% (Schenker & Granat 1982). More recently (Table 1), the fetal loss has fallen to 26% overall and 15% when the diagnosis of phaeochromocytoma was made during the antenatal period.

Antenatal recognition of a phaeochromocytoma is most important because of the improved maternal and fetal outcome. There is considerable room for improvement as phaeochromocytoma was diagnosed antenatally in only 26 (53%) of the 49 pregnancies in the present review (Table 1) compared with 25% before 1969 and 52% in the period 1969–1979 (Schenker & Granat 1982). Almost all non-pregnant patients with a phaeochromocytoma have hypertension, most have either headache, excessive perspiration or palpitations, and many have all three symptoms occurring in paroxysms (Gifford *et al.* 1964; Kaplan 1986). Details of the 42 patients reported in the years 1980–1987 and our five patients are summarized in Table 1. Most of these patients had fluctuating, often severe, hypertension associated with a variety of symptoms and signs, the commonest being headache, excessive perspiration, palpitations and tachycardia. Although most patients with a phaeochromocytoma in pregnancy present with symptomatic hypertension and, in most, clues for early diagnosis could be detected in retrospect (Schenker & Granat 1982), the occurrence of both hypertension and classical symptoms is less frequent than in the non-pregnant patient (Table 2). These tumours may also present with a wide variety of other symptoms and signs, including arrhythmias, postural hypotension, chest or abdominal pain, abdominal mass, unusual responses to drugs which affect the release and actions of circulating catecholamines, visual disturbances, convulsions, sudden collapse and sudden death. Hypertension may be absent.

Possibly the most important aid to early diagnosis is to think of phaeochromocytoma. Hypertension is very common in pregnancy, and patients must be selected for investigation. Phaeochromocytoma should be excluded in all pregnant women with severe or intermittent hypertension, with hypertension associated with the paroxysmal symptoms noted above; with hypertension in the first half of pregnancy; with hypertension and abnormal glucose tolerance or diabetes mellitus; with suspected thyrotoxicosis; and in cases of sudden collapse in the obstetric patient. It is interesting to note that all five of our patients had features in their history which pointed towards the diagnosis. In the first patient, a hypertensive crisis following caesarean section resulted in the correct diagnosis, although suspicion should have been aroused earlier in view of her chronic hypertension and symptoms of chest heaviness. The third and fourth patients presented with hypertension and typical symptoms (patient 3—paroxysms of tachycardia, anxiety, sweating; patient 4—recurrent headache) leading to an early diagnosis of phaeochromocytoma. In the fifth patient, the occurrence of hypertension and

Table 1. Data on patients with phaeochromocytoma associated with pregnancy reported 1980–1987

Study	Age/ Parity	Diagnosis	Localization/ Tumour site	Removal (gestational age)	Maternal outcome	Fetal outcome	Comments
1 Badui *et al* (1982)	32/?	Postpartum	— L adrenal and para-aortic	—	Died (CVA)	Alive, CS after 8 months	
2. Badui *et al.* (1982)	22/?	Postpartum	— R adrenal	—	Died (hypotension)	Alive, CS after 8 months	
3 Bahta *et al* (1987)	21/3	Postpartum	— Aortic bifurcation +intrathoracic	Laparotomy Thoracotomy (postpartum)	Alive	IUD in 2nd trimester	Malignant phaeo.
4 Bolli *et al* (1981)	26/0	Antenatal	At CS/Organ of Zuckerkandl	At CS	Alive	NND aged 3 h, CS 34 weeks	
5. Chatterjee & Parekh (1985)	25/1+2	Antenatal	Aortography (antepartum)/Aortic bifurcation	Laparotomy (24 weeks)	Alive	IUD 23 weeks	
6. Chodankar *et al.* (1982)	24/3	Autopsy	— Bilateral adrenal	—	Died undelivered (CVA)	IUD 32 weeks	MEN IIa
7 Davies & Navaratnarajah (1984)	22/0	Postpartum	Arteriogram, CT scan (postpartum)/L extra-adrenal and aortic bifurcation	Laparotomy (postpartum)	Alive	Stillbirth, FD 33 weeks, 2080 g	
" "	23/1	Antenatal	Postpartum/L renal hilum and inferior to pancreas	Laparotomy (postpartum)	Alive	Alive, FD 37 weeks, 2830 g	Recurrent phaeo.
8 Devoe *et al* (1986)	24/0+1	Antenatal	CT scan (postpartum)/R. lung coeliac axis	Thoracotomy Laparotomy (postpartum)	Alive	Alive, CS 33 weeks, 1450 g, F	Recurrent phaeo.
9. Epstein *et al* (1985)	28/1+1	Postpartum	CT scan (post-partum)/L. adrenal	Laparotomy (postpartum)	Alive	Alive, NVD, 3400 g, F	MEN IIb
10. Feldman (1985)	29/2	2 years postpartum	CT scan (2 years postpartum)/L adrenal	Laparotomy (2 years postpartum)	Alive	Stillbirth, CS 36 weeks	
11 Freier *et al* (1980)	?	Antenatal	?/Bilateral adrenal	Laparotomy/ hysterotomy (2nd trimester)	Alive	Termination, SGA	MEN IIb
12 Fudge *et al* (1980)	29/1	Antenatal	At CS/R adrenal	At CS	Alive	Alive, CS at term, 4000 g, F	

Table 1. Continued

Study	Age/ Parity	Diagnosis	Localization/ Tumour site	Removal (gestational age)	Maternal outcome	Fetal outcome	Comments
13 Galletley *et al.* (1983)	24/1	Antenatal	At CS/L. extra-adrenal	At CS	Alive	Alive, CS 38 weeks, 2600 g, M	
14. Greenberg *et al.* (1986)	31/0+2	Antenatal	MRI (antenatal)/ Aortic bifurcation	At CS	Alive	Alive, CS 37 weeks	
15. Griffin *et al.* (1984)	24/3+1	Antenatal	At CS/L. adrenal	At CS	Alive	Alive, CS 35 weeks, 2980 g, F	
16. Khan *et al* (1984)	29/0+2	Postpartum	US (postpartum)/ Bilateral adrenal	Laparotomy (postpartum)	Alive	?Alive	Brother with neurofibromatosis
17. Kleiner *et al.* (1982)	34/7	Postpartum	CT scan (postpartum)/L extra-adrenal	Laparotomy (postpartum)	Alive	Alive, CS 37 weeks, 2800 g, F	
18. Levin *et al.* (1983)	38/1	Antenatal	Abdominal tumour palpated/Presacral	Laparotomy (14 weeks)	Alive	Alive, NVD 38 weeks, 3289 g, M	
19. Lowe *et al.* (1987)	31/3	Postpartum	CT scan, angiography/L. adrenal	Laparotomy (postpartum)	Alive	Alive, CS 40 weeks	
20. Meyers (1982)	35/3	Postpartum	At laparotomy/R. adrenal	Laparotomy (postpartum)	Alive	Alive, CS	
21. Mitchell *et al* (1987)	29/1	Antenatal	US/R. adrenal	Laparotomy (24 weeks)	Alive	Alive, CS 39 weeks, 2977 g, M	
22. Montminy & Teres (1983)	36/0+3	Autopsy	— Bilateral adrenal	—	Died undelivered (shock after i v. promethazine)	IUD 33 weeks during acute crisis	
23. Moraca-Kvapilova *et al.* (1985)	30/1+1	Postpartum	Abdominal US, CT scan (postpartum)/ Bilateral adrenal	Laparotomy (postpartum) Thyroidectomy (medullary ca)	Alive (CVA)	Alive, CS 35 weeks, 3780 g, M	MEN IIa
24. Mulcahy *et al.* (1984)	29/0	Postpartum	CT scan (postpartum)/L. adrenal	Laparotomy (postpartum)	Alive	IUD 25 weeks	
25 Mulcahy *et al* (1984)	20/0	Postpartum	CT scan (postpartum)/R. adrenal	Laparotomy (postpartum)	Alive	Miscarriage 20 weeks	
" "	21/0+1	Antenatal	CT scan (antenatal)/L. adrenal	Laparotomy (15 weeks)	Alive	Alive	Recurrent phaeo

Table 1. Continued

Study	Age/ Parity	Diagnosis	Localization/ Tumour site	Removal (gestational age)	Maternal outcome	Fetal outcome	Comments
26. Ober (1983)	20/?	Antenatal	US, CT scan (antenatal)/L adrenal	Laparotomy (2nd trimester)	Alive	Alive	Hyperthyroidism
27. Parsons *et al* (1984)	19/1+1	Autopsy	— L. extra-adrenal	—	Died 6 h postpartum	Alive, NVD 38 weeks, 2600 g, M	
28. Pinaud *et al.* (1985)	25/0	Antenatal	Abdominal US (antenatal)/Bilateral adrenal	At CS	Alive	Alive, CS 36 weeks, 2240 g, M	Recurrent phaeo.
29. Pollock *et al.* (1986)	24/?0	Antenatal	CT scan (antenatal)/R. adrenal	Laparotomy (postpartum)	Alive	Alive, CS 36 weeks, SGA	
30 Richart (1980)	29/2+2	Autopsy	R. adrenal	—	Died on 19th postpartum day	Alive, CS 37 weeks, 3320 g, F	
31. Stanley *et al.* (1985)	29/2+1	Autopsy	— R adrenal	—	Died 2 h postpartum	Stillbirth, CS term	
32. Stanley *et al.* (1985)	20/0	Antenatal	CT scan (antenatal)/ Organ of Zuckerkandl	At CS	Alive	Alive, CS 36 weeks	
33. Stenstrom & Swolin (1985)	22/0	Antenatal	Aortography (antenatal)/R. adrenal	At CS	Alive	Alive, CS 38 weeks	
34. Stenstrom & Swolin (1985)	29/1	Antenatal	At CS/R. adrenal	At CS	Alive, later skeletal metastases	Alive, CS 38 weeks	Malignant phaeo.
35. Stenstrom & Swolin (1985)	24/1	Antenatal	Aortography (antenatal)/R. adrenal	At CS	Alive	Alive, CS 39 weeks, 4720 g, M	
36 Stonham & Wakefield (1983)	15/0	Antenatal	CT scan (postpartum)/L. extra-adrenal	Laparotomy (postpartum)	Alive	Alive, CS 36 weeks, 3500 g, M	Recurrent phaeo
37. Stonham & Wakefield (1983)	27/2	Antenatal	— ?	—	Alive, refused further investigation	Alive, CS 37 weeks, 2600 g, F	Recurrent phaeo
38 Vellar *et al* (1985)	30/?	Postpartum	Selective venous sampling/L. adrenal	Laparotomy (postpartum)	Alive	Alive, NVD 40 weeks	
39. Vellar *et al.* (1985)	32/?	? postpartum	Angiography/L. adrenal	Laparotomy (?postpartum)	Alive	Alive, CS 31 weeks	
40. Venuto *et al.* (1984)	27/0	Antenatal	CT scan (postpartum)/L adrenal	Laparotomy (postpartum)	Alive	Alive, CS 37 weeks, 2865 g, M	
41 Wagener *et al* (1981)	30/0	Antenatal	US/L. adrenal	Laparotomy and hysterotomy (18 weeks)	Alive	IUD 18 weeks	

Table 1. Continued

Study	Age/ Parity	Diagnosis	Localization/ Tumour site	Removal (gestational age)	Maternal outcome	Fetal outcome	Comments
42. Wolfman (1982)	20/?	Antenatal	US, CT scan (2nd trimester)/L adrenal	Laparotomy (antenatal)	Alive	Alive, NVD	
Present study							
43 Patient 1	39/2	Postpartum	CT scan, femoral aortogram, vena caval sampling/R. extra-adrenal	Laparotomy (postpartum)	Alive	Alive, CS 28 weeks, 1160 g, M	Malignant phaeo.
44. Patient 2	37/0	Autopsy	— R adrenal	—	Died undelivered	Died, 2500 g, M	Neurofibromatosis
45. Patient 3	24/0	Antenatal	US, digital angiography/R. adrenal	Laparotomy (23 weeks)	Alive	Alive, NVD 38 weeks, 2920 g, F	
46 Patient 4	39/1+2	Antenatal	US, CT scan/ Bilateral adrenal	Laparotomy (16 weeks)	Alive	Alive, NVD 37 weeks, 3180 g, M	
47. Patient 5	28/1	Postpartum	CT scan/L. extra-adrenal	Laparotomy (postpartum)	Alive	Alive, CS 38 weeks, 3000 g, M	

CT, Computerized tomography; US, ultrasound; R., right; L., left; CVA, cardiovascular accident; NVD, normal vaginal delivery; CS, caesarean section; FD, forceps delivery; SGA, small for gestational age, MEN, multiple endocrine neoplasia; IUD, intrauterine death; NND, neonatal death; M, male, F, female; MRI, magnetic resonance imaging; phaeo., phaeochromocytoma.

Table 2. Frequency of the most common symptoms and signs of phaeochromocytoma

	Kaplan (1986)*	Schenker & Granat (1982)†	Present study‡
Hypertension	98%	>80%	89%
Headache	80–85%	>60%	43%
Palpitations and/or tachycardia	60–65%	>30%	40%
Sweating	65–70%	>30%	28%

*Pooled data from series of non-pregnant patients.
†Data from 139 cases of phaeochromocytoma in pregnancy.
‡Data from 47 cases of phaeochromocytoma in pregnancy.

subsequently a myocardial infarction in a previously healthy young woman following her first delivery might have suggested the true diagnosis at an earlier stage. The second patient presented with sudden collapse without previous hypertension. Phaeochromocytoma was suspected at the time of her crisis, but she died before the diagnosis could be established. She had had neurofibromatosis for many years. Phaeochromocytoma occurs in about 1–2% of patients with neurofibromatosis (Kalff *et al.* 1982) and the association of phaeochromocytoma, multiple neurofibromatosis (von Recklinghausen's disease) and pregnancy has been reported previously (Geisler & Lloyd 1963; Humble 1967; Smith 1973, Fledelius & Eldrup-Jorgensen 1977). Although her death was probably unavoidable once she had presented clinically, screening for excess catecholamine secretion during pregnancy might have detected her tumour. There are several possible methods of screening normotensive patients at risk of phaeochromocytoma (these would usually be from families with MEN-II): good results have been obtained in non-pregnant subjects by measuring plasma adrenaline levels after bicycle exercise (Telenius-Berg *et al.* 1987). We have no experience of this test or the recently advocated ratio of urinary epinephrine to norepinephrine (Gagel *et al.* 1988).

Phaeochromocytoma may occur as simple familial phaeochromocytoma or in association with medullary carcinoma of the thyroid gland and parathyroid adenomas as multiple endocrine neoplasia (type II) syndrome, MEN-II (Kaplan 1986). Six cases of pregnancy associated with phaeochromocytoma as part of MEN-II have been reported (Paloyan *et al.* 1970; Raynor & Sowden 1975; Freier *et al.* 1980; Chodankar *et al.* 1982; Epstein *et al.* 1985; Moraca-Kvapilova *et al.* 1985). Our fourth patient had bilateral phaeochromocytomas and a thyroid nodule, and we had suspected MEN-II initially, but this was disproved by the absence of a thyroid medullary carcinoma.

The clinical diagnosis of phaeochromocytoma requires confirmation. Estimation of urinary catecholamines in a properly collected 24-h urine sample, preferably obtained during or immediately following a hypertensive episode, will establish the diagnosis in almost all cases. Newer assay methods using high-pressure liquid chromatography or the catechol-*o*-methyltransferase radioenzymatic technique have considerably improved the diagnostic accuracy. Pharmacological tests such as the phentolamine suppression test are unnecessary and have been associated with maternal and fetal death (Roland 1959).

Once the diagnosis of phaeochromocytoma has been established by biochemical investigation, pre-operative tumour localization is desirable. Ninety per cent of phaeochromocytomas arise in the adrenal medulla and 98% occur within the abdomen (Falterman & Kreisberg 1982). They may be multiple. Bilateral adrenal tumours occur in 10% of cases: this incidence is increased in familial cases, particularly in the MEN-II syndrome (Falterman & Kreisberg 1982). In the 47 patients reviewed (Table 1) the tumour site was right adrenal in 12 (25%), left adrenal in 12 (25%), bilateral adrenal in 8 (17%), intra-abdominal extra-adrenal in 15 (32%)—one of these patients also had a left adrenal tumour, and two also had intrathoracic tumours. The tumour site was unknown in one patient.

Methods of tumour localization are restricted during pregnancy. Abdominal ultrasound is safe, but display of the lower abdomen may be inadequate. Computed tomography can localize accurately the majority of intra-abdominal phaeochromocytomas and has been used in pregnancy (Wolfman 1982; Ober 1983; Mulcahy *et al.* 1984; Stanley *et al.* 1985; Pollock *et al.* 1986; our patient no. 4). To date, no adverse fetal effects have been reported. Magnetic resonance imaging has been used recently during pregnancy (Greenberg *et al.* 1986). It produces high quality images and has the advantage that it does not employ ionizing radiation.

Treatment with an alpha-adrenergic blocking agent to control hypertension should be started as soon as the diagnosis of phaeochromocytoma has been established, or sooner if there is a strong clinical suspicion. The drug of choice is phenoxybenzamine (Wheeler *et al.* 1982), an irreversible alpha-adrenoceptor antagonist which protects against the effects of the sudden release into the circulation of large amounts of catecholamines from the tumour. It can be given orally, starting with 10 mg twice daily and gradually increasing the dose in increments of 10–20 mg daily until hypertension is controlled and other symptoms and signs eliminated. This may take from 10 to 14 days to achieve (Wheeler *et al.* 1982). Phenoxybenzamine has been used during pregnancy in several of the reported cases of phaeochromocytoma and to date there is no evidence of adverse fetal effects.

Prazosin (a post-synaptic alpha-adrenoceptor blocking agent) (Venuto *et al.* 1984; Pinaud *et al.* 1985; Devoe *et al.* 1986) and labetalol (an alpha- and beta-adrenoceptor blocking agent) (Galletly *et al.* 1983; our patient no. 4) have also been used during pregnancy without adverse fetal effects. Alpha-methyl paratyrosine inhibits tyrosine hydroxylase and reduces catecholamine synthesis. There is one report of its use during pregnancy (Devoe *et al.* 1986). Experience during pregnancy with these newer drugs in phaeochromocytoma is limited and we do not consider them first-line options.

Beta-blockade should not be used without prior alpha-blockade as unopposed alpha-adrenergic activity may lead to generalized vasoconstriction and a steep rise in the blood pressure (Wheeler *et al.* 1982). After adequate alpha-blockade has been established, beta-blockers may be used to control tachycardia and arrhythmias. Propranolol is generally given; our usual dosage is between 60 and 120 mg daily. The fetal outcome has been good in most pregnancies in which propranolol has been used (Galletly *et al.* 1983; Stonham & Wakefield 1983; Greenberg *et al.* 1986; Mitchell *et al.* 1987), although in two pregnancies fetal growth retardation occurred and was the reason for termination of pregnancy in one (Freier *et al.* 1980), and was associated with intrauterine death in the other (Chatterjee & Parekh 1985).

The definitive treatment of phaeochromocytoma is surgical removal. When the diagnosis is made before 23 weeks gestation, the tumour should be removed once adrenergic blockade has been achieved. Although up until 1979 only one fetus survived out of the five pregnancies in which surgical intervention was undertaken before 24 weeks gestation (Schenker & Granat 1982) there has been a successful fetal outcome in seven of the eight more recently reported cases (Wolfman 1982; Levin *et al.* 1983; Ober 1983; Mulcahy *et al.* 1984; Mitchell *et al.* 1987; our patients nos 3 and 4). In the eighth case (Freier *et al.* 1980) the pregnancy was electively terminated at the time of laparotomy because of fetal growth retardation. After 24 weeks gestation uterine size makes abdominal exploration and access to the tumour difficult unless the woman is first delivered. Optimum results are obtained if surgery is delayed until fetal maturity is reached. Then, under adrenergic blockade, elective caesarean section may be performed, followed immediately by exploration for the tumour (Burgess 1979). The anaesthetic management of phaeochromocytoma is most important and has been discussed elsewhere (Burgess *et al.* 1978; Galletly *et al.* 1983; Stonham & Wakefield 1983; Pinaud *et al.* 1985; Mitchell *et al.* 1987). In the past, vaginal delivery carried a higher maternal mortality (31%) than caesarean section (19%) (Schenker & Granat 1982). Of the 16 women in the present review, where a phaeochromocytoma was diagnosed but not removed antenatally, delivery was by caesarean section in 15, with concurrent resection of the tumour in 10, removal at a later date in four and one patient refused further investigation (Table 1); there was one neonatal death (Bolli *et al.* 1981) and no maternal deaths. Where phaeochromocytoma was unrecognized before delivery, acute hypertensive crises or shock occurred in several patients during or shortly after both caesarean section and vaginal delivery, causing maternal death after caesarean section in two of 12 patients (17%) (Richart 1980; Stanley *et al.* 1985) and following vaginal delivery in one of eight (13%) (Parsons *et al.* 1984). Two other maternal deaths occurred after caesarean section and postpartum confirmation of phaeochromocytoma but before surgical treatment (Badui *et al.* 1982). Three other patients with unrecognized phaeochromocytoma died during the antenatal period (Chodankar *et al.* 1982; Montminy & Teres 1983; our patient no. 2).

Because of the possibility of incomplete removal of tumour, recurrences or metastases, which may not develop for many years (Schenker & Granat 1982), careful postoperative follow-up with measurements of urinary catecholamines is essential. Malignancy occurs in about 10% (Falterman & Kreisberg 1982) and is more common when the tumour site is extra-adrenal (Melicow 1977). Fourteen patients with recurrent or metastatic phaeochromocytoma in association with pregnancy have been reported (Schenker & Granat 1982; Table 1).

Phaeochromocytoma remains a rare but important cause of hypertension and cardiovascular collapse in pregnancy. Although the maternal and fetal outcomes have improved, an unsuspected phaeochromocytoma may still have disastrous consequences. A high index of clinical suspicion must be maintained to achieve an early diagnosis. All pregnant women with hypertension associated with any unusual features, particularly those with severe or symptomatic hypertension, especially those with headache, excessive sweating or palpitations, or with a family history of phaeochromocytoma or associated syndromes, should have routine screening of 24 h urinary catecholamine levels. Once the diagnosis has been confirmed, computerized tomography or magnetic resonance imaging offer the best methods of tumour localization. Adequate alpha-blockade is essential and beta-blockade may also be required. Tumour resection before 28 weeks gestation has been shown to have a good fetal outcome. In later pregnancy, delivery by caesarean section when fetal maturity is reached, followed by tumour resection, either at the time of caesarean section or later, is best. Early diagnosis is the key to a better prognosis in phaeochromocytoma associated with pregnancy.

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Oxybutinin versus propantheline in the management of detrusor instability. A patient-regulated variable dose trial

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Summary. Two of the principal drugs used to treat detrusor instability, oxybutinin hydrochloride and propantheline bromide, were compared using clinical and urodynamic outcome measures in a randomized crossover trial with a patient-regulated variable dose regimen. Of the 23 women in the trial, 14 reported subjective improvement during treatment with oxybutinin hydrochloride compared with 11 during treatment with propantheline bromide. Apart from a greater increase in the maximum cystometric capacity with oxybutinin, there were no other objective differences between the two drugs. Oxybutinin significantly delayed the first desire to void, increased the maximum cystometric capacity and reduced the maximum detrusor pressure rise on filling. Propantheline significantly increased the maximum cystometric capacity and reduced the maximum detrusor pressure rise on filling. Three patients stopped treatment due to side-effects.

Detrusor instability is a recognized cause of frequency, nocturia, urgency, and urge incontinence in women and occurs in up to 37% of women attending an incontinence clinic (Cardozo 1984). The many different treatments and the poor rate of success reflect the uncertain aetiology of detrusor instability and the relative lack of response to drug therapy such as anticholinergic preparations. Oxybutinin hydrochloride and propantheline bromide are both potent, orally active, anticholinergic preparations which are used to treat frequency and urge incontinence due to detrusor instability. The maximum therapeutic dose of each is limited by muscarinic parasympathetic blockade of smooth muscle and salivary glands. The side-effects include constipation, dry mouth and blurring of the vision. A fixed dose comparison of the two drugs is thus invalid unless these side-effects are considered. To date, there is no objective study comparing these two drugs or using a variable dose regimen.

The present study set out to determine whether oxybutinin or propantheline is more effective. It allowed the patients to determine the maximum dose they could tolerate, through titration of the therapeutic effects against the production of side-effects.

Subjects and methods

This randomized, single-blind crossover trial included 23 women who were attending the uro-

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Table 1. Patient data in the two groups

	Group 1 (n=10) Mean	Group 2 (n=13) Mean	95% CI of difference
Age (years)	39·6	44·5*	−16·3 to 6·5
Peak flow rate (ml/s)	25·0	26·2*	−12·9 to 10·5
Residual urine volume (ml)	26·1	26·5*	−35·9 to 35·1
Volume at first desire to void (ml)	95·0	87·3*	−45·1 to 60·5
Maximum cystometric capacity (ml)	324	359*	−111 to 41·3
Maximum detrusor pressure rise at cystometry (cm H_2O)	35	32*	−12·9 to 18·9
Maximum voiding pressure (cm H_2O)	53·2	49*	−15·8 to 23·1
Daytime frequency (total voids over 3 days)	38·6	29·1**	
range	(16–43)	(18–44)	
Nocturia (total voids over 3 nights)	5	7**	
range	(1–12)	(2–9)	

Significance of difference *$P>0{\cdot}05$ Student's t-test, **$P>0{\cdot}05$ Mann–Whitney U-test.

dynamic clinic of St George's Hospital with symptoms due to idiopathic detrusor instability. Their informed consent was obtained beforehand. Each patient underwent a full clinical examination, which included a neurological assessment. Urodynamic assessment before the trial included twin-channel, subtracted cystometry and cystourethroscopy to exclude intravesical and urethral pathologies; all women had sterile urine. Their mean age was 42·4 years (range 24–66 years).

A 3-day urinary diary was completed before and at the end of each treatment arm to record urinary frequency and nocturia. Each patient also completed linear analogue scales to record the severity of the incontinence and the potential side-effects of constipation, dry mouth and blurred vision. Excepting one patient who had multiple sclerosis diagnosed during the study, all were neurologically normal.

A computer-generated randomization code was used to allocate the women to receive treatment either first with oxybutinin followed by propantheline or first with propantheline followed by oxybutinin. Ten women were treated first with oxybutinin, 5 mg three times daily, the other 13 women were treated first with propantheline bromide, 15 mg three times daily. Each course lasted 1 month, with 1 week separation between the two drug therapies, as a wash-out period. The women were cautioned about the potential side-effects and were advised to protect themselves against constipation by increasing the fibre content of their diet They were asked at the end of each week to increase the dose by 5 mg or 15 mg respectively, if they had neither subjective improvement in symptoms, nor had significant side-effects. If at any time they had side-effects which outweighed the therapeutic benefit they were asked to reduce the dose The urodynamic unit was informed if any patient ceased drug therapy. Once the optimal dose was found, the patients continued on this until the end of the treatment course. The 3-day urinary diary was completed and cystometry repeated unless treatment had been discontinued or the women felt subjectively that there had been no change in their urinary symptoms and were not prepared to have cystometry repeated. A 1-week wash-out period followed and during the last 3 days a diary was again completed The second course of treatment followed and a urinary diary was completed over the last 3 days. Cystometry was repeated using the same criteria as after the first phase of the study. The linear analogue scales of the severity of incontinence and side-effects were completed with each urinary diary.

The data from the cystometry tracings, the four urinary diaries and the linear analogue scales were analysed using Student's t-test, Student's paired t-test, Mann–Whitney U-test and Wilcoxon matched pairs, signed rank tests as appropriate.

Results

The two groups were comparable before treatment. There were no statistically significant differences in age, daytime voiding frequency, nocturia, peak flow rate, residual urine volume,

Table 2. Data pretreatment versus treatment with oxybutinin

	Pretreatment Mean	Oxybutinin Mean	*n*	Student's paired *t*-test probability of difference (*P*)		95% CI
Peak flow rate (ml/s)	28	24	17	>0·05		−3·4 to 11·4
Residual urine volume (ml)	32·2	38·1	18	>0·05		−30 to 18·3
First desire to void (ml)	97·9	179·2	19	<0·05		−14·6 to 16·3
Maximum cystometric capacity (ml)	357	485	19	<0·005		−211 to −45·4
Maximum pressure rise (cm H_2O)	35·1	19·7	19	<0·005		5·76 to 25·0
Maximum voiding pressure (cm H_2O)	53·6	37·7	14	<0·01		5·52 to 26·2
				Wilcoxon signed rank test		Probability of difference
				T_1	T_2	(*P*)
Daytime frequency (total voids over 3 days)	32·4	26·5	20	125	11	<0·01
range	(14–53)	(11–46)				
Nocturia (total voids over 3 nights)	4·0	2·6	20	91·5	28·5	>0·05
range	(0–12)	(0–7)				
Incontinence (linear analogue scale)	39·8	17·6	20	110	10	<0·01
range	(0–108)	(0–87)				
Side-effects (linear analogue scale)						
Dry mouth	7·1	29·8	20	16	174	<0·01
range	(0–37)	(0–58)				
Constipation	4·5	10·1	20	17	61	>0·05
range	(0–21)	(0–35)				
Blurred vision	4·3	12·1	20	13	107	<0·01
range	(0–40)	(0–44)				

volume at which the first desire to void occurred, maximum cystometric capacity, maximum detrusor pressure rise on filling or maximum voiding pressure, using Student's *t*-test for difference (Table 1). There were no statistically significant differences in day and night-time voiding patterns between the two groups (Mann–Whitney *U*-test).

Two women in the group treated first with oxybutinin were unable to tolerate either oxybutinin or propantheline; therefore they did not have cystometry. One of them declined to complete a urinary diary at the end of the first 'treatment' period, but both completed diaries at the end of the second 'treatment' period. These diaries were included in the analysis since the intention to treat had been established. Another woman in this group developed severe blurring of vision during the first treatment with oxybutinin. She had cystometry and completed her diary but was found to have pathological cupping of the optic discs and was thereafter excluded from further participation in the trial. Two women felt that they were subjectively unchanged with either preparation, and declined to complete any diaries during treatment. Cystometry was not performed in these women but during the initial cystometry one had experienced the first desire to void at a bladder volume of 100 ml, the other at 30 ml. The maximum detrusor pressure rise in one of these women was 20 cm H_2O, and in the other it was 18 cm H_2O. It may have been that their symptoms were due to a different pathology.

Table 3. Data pretreatment versus treatment with propantheline

	Pretreatment Mean	Propantheline Mean	n	Student's paired t-test probability of difference (P)		95% CI
Peak flow rate (ml/s)	28·6	24·5	16	>0·05		−0·57 to 8·3
Residual urine volume (ml)	32·4	16·5	17	>0·1		−8·27 to 40·0
First desire to void (ml)	101	167	18	>0·05		−143 to 10·7
Maximum cystometric capacity (ml)	365	426	18	>0·1		−147 to 24·9
Maximum pressure rise (cm H_2O)	33·4	24·2	18	<0·05		2·21 to 16·3
Maximum voiding pressure (cm H_2O)	53·9	40·8	13	<0·01		4·65 to 21·5
				Wilcoxon signed rank test T_1	T_2	Probability of difference (P)
Daytime frequency (total voids over 3 days)	30·3	27·3	21	136	54	>0·05
range	(15–57)	(13–39)				
Nocturia (total voids over 3 nights)	4·2	3·6	21	93	60	>0·05
range	(0–12)	(0–16)				
Incontinence (linear analogue scale)	29·0	32·6	21	74	62	>0·05
range	(0–101)	(0–116)				
Side-effects (linear analogue scale)						
Dry mouth	13·3	18·4	21	50·5	85·5	>0·05
range	(0–46)	(0–49)				
Constipation	9·0	9·3	21	43·5	47·5	>0·05
range	(0–46)	(0–46)				
Blurred vision	5·9	16·2	21	18	102	<0·05
range	(0–40)	(0–49)				

The pretreatment data were then compared with those obtained at the end of the first wash-out period. Cystometry was not performed at the end of the wash-out period and so only the diaries could be compared. There were no significant differences in the linear analogue assessments of the symptoms of dry mouth, blurred vision or constipation between the two groups. There was no statistically significant difference in the total number of daytime or night-time voids or in the linear analogue scores of the severity of the incontinence (Wilcoxon, signed rank test for difference). From this it was assumed that there was no carry-over effect of the first treatment into the next and the data from the two treatment arms could be combined.

The data from the two treatment groups were combined and the values obtained were first compared with the pretreatment data (Tables 2 and 3) and then between the two groups. During treatment with oxybutinin, statistically significant improvement was found in the volume at which the first desire to void occurred, the maximum cystometric capacity, maximum detrusor pressure rise, daytime voiding frequency and severity of incontinence. This was achieved at the expense of a significant decrease in the maximum voiding pressure and significant worsening in the side-effects of dry mouth and blurred vision. Treatment with propantheline significantly increased the maximum cystometric capacity and decreased the maximum pressure rise found at cystometry. The cost of this was a significant decrease in the maximum voiding pressure with a significant deterioration in the clarity of vision.

When the cystometry and questionnaire data obtained during treatment with oxybutinin and propantheline were compared (Table 4) the only statistically significant difference found was an increase in the maximum cystometric capacity during treatment with oxybutinin.

Overall, 14 patients said that they were improved subjectively whilst taking oxybutinin, compared with 11 who were improved during treatment with propantheline. This is not statistically significant (χ^2-test for difference).

The median total daily dose of oxybutinin hydrochloride tolerated was 15 mg (range 7·5–30 mg) and that of propantheline bromide was 90 mg (range 45–145 mg). Whilst taking these doses both oxybutinin and propantheline gave a significant deterioration in the symptom of blurred vision. Whilst taking oxybutinin the women were prepared to accept a significant deterioration in the symptom of dry mouth to achieve a significant improvement in the severity of their incontinence. This was not found during treatment with propantheline.

Discussion

Oxybutinin has been found by many clinicians to be a useful and effective drug in the management of symptoms due to detrusor instability (Moisey *et*

Table 4. Data oxybutinin versus propantheline

	Oxybutinin *vs* propantheline Difference of means	*n*	Student's paired *t*-test probability of difference (*P*)	95% CI
Peak flow rate (ml/s)	−0·57	14	>0·05	−7·87 to 6·73
Residual urine volume (ml)	22·5	16	>0·05	−7·42 to 52·4
First desire to void (ml)	−5·3	18	>0·05	−52·2 to 41·7
Maximum cystometric capacity (ml)	50·6	18	<0·05	6·80 to 94·3
Maximum pressure rise (cm H_2O)	−4·28	18	>0·05	−14·2 to 5·60
Maximum voiding pressure (cm H_2O)	−2	13	>0·05	−12·0 to 8·04

			Wilcoxon signed rank test		Probability of difference (*P*)
			T$_1$	T$_2$	
Daytime frequency (total voids over 3 days)	−1·15	20	58·5	94·5	>0·05
range	(−14 to 9)				
Nocturia (total voids over 3 nights)	−0·4	20	56	64	>0·05
range	(−10 to 3)				
Incontinence (linear analogue scale)	−16·6	20	41·5	94·5	>0·05
range	(−111 to 67)				
Side-effects (linear analogue scale)					
Dry mouth	11·8	20	131·5	39·5	>0·05
range	(−44 to 44)				
Constipation	0·35	20	60·5	44·5	>0·05
range	(−43 to 32)				
Blurred vision	−3·75	20	51	85	>0·05
range	(−43 to 25)				

al. 1984; Cardozo *et al.* 1987) and detrusor hyperreflexia (Hennessy *et al.* 1988). Objective urodynamic studies in a double-blind trial confirm these benefits, although Meyhoff *et al.* (1981) found that a placebo in this trial could produce up to 47% improvement in symptoms. It was therefore felt important to exclude a placebo effect and to compare oxybutinin with the most commonly used anti-cholinergic drug used for detrusor instability, namely propantheline. There are no published studies directly comparing these two drugs in man, although Fredericks *et al.* (1978) have studied them in rabbits.

As oral absorption of tertiary and quaternary amines is poor and therefore dose responses uncertain, the procedure of dose titration for the individual patient's requirements has been adopted (Massey & Abrams 1984). This allows the patient to increase the dose in relation to side-effects and cure.

Although oxybutinin has been effective in decreasing the symptoms of frequency and incontinence, when compared with the pretreatment state, it was disappointing that a clear difference between oxybutinin and propantheline did not emerge. Only 23 patients could be recruited within the time period allocated for the study: the differences between oxybutinin and propantheline may become more obvious within a larger trial which might be more appropriate to compare these two drugs.

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45 X Turner's syndrome in association with polycystic ovaries. Case report

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Case report

The patient, the second of three siblings, was born on 25 November 1971 to unrelated parents after induction of labour at 38 weeks gestation for maternal weight loss and suspected placental insufficiency (low oestrogen excretion). Her birthweight was 3·3 kg. She was noted to be of short stature from 11 years. After initially regular 28-day cycles from menarche at age 12 years, her periods became heavy and prolonged. She was referred to Professor Tanner at the Hospital for Sick Children, Great Ormond Street, early in 1985 for investigation. He noted typical features of Turner's syndrome—short stature (142 cm), webbing of the neck, and cubitus valgus—although there were signs of sexual maturation: stage 5 breasts and pubic hair; axillary hair, however, was only stage 1. Bone age was 16 years. Investigations showed lymphocyte karyotype 45 X with no evidence of mosaicism. She was referred to us for further investigation of the ovarian status, and was first seen in June 1985.

Her cycle length now varied between 1 and 4 months with associated dysmenorrhoea. She also had intermittent severe abdominal cramps, and occasional hot sensations.

Examination showed no change from Professor Tanner's findings (Fig. 1). She was normotensive with no evidence of any cardiovascular anomaly.

Investigations (Table 1) confirmed lymphocyte karyotype 45 X, with normal gonadotrophin, steroid and thyroid hormone concentrations. Pelvic ultrasound showed an adult uterus with a thick endometrium, a 38×33 mm cyst on the left ovary and an enlarged right ovary with a polycystic pattern (Fig. 2).

Treatment was commenced with a 5-day course of medroxyprogesterone (10 mg/day) to induce endometrial shedding, followed by a combined oral contraceptive pill (Brevinor) with the aim of suppressing gonadotrophin drive to the cyst. Subsequent scans showed resolution of the cyst and that the underlying follicular pattern in the left ovary (50×20×34 mm) was polycystic also. The right ovary was slightly larger at 36×34×28 mm (Fig. 3). She continued to have regular withdrawal bleeds with minimal dysmenorrhoea. In January 1986, she had one episode of intermenstrual lower abdominal pain associated with a bright red vaginal blood loss. A pelvic scan showed 'suppressed' polycystic ovaries with no cyst, but some fluid in the pouch of Douglas, suggestive of a recently ruptured cyst. In October 1986, she stopped treatment because of headaches. She had a single withdrawal bleed and has since been amenorrhoeic. Follow-up ultrasound in November 1986 showed a 4·0×4·0×2·6 cm cyst on the right ovary, the left remaining polycystic with a maximum follicular diameter of 4 mm; the endometrium was thickened to 12 mm.

Her mother, aged 41, and both her elder and younger sisters, aged 17 and 6 respectively, all with 46 XX karyotype, had pelvic scans and all showed the polycystic ovarian pattern, the mother having had a hysterectomy at age 38 for menorrhagia, the elder sister having had irregular, heavy menses from menarche until starting to take the combined oral contraceptive pill,

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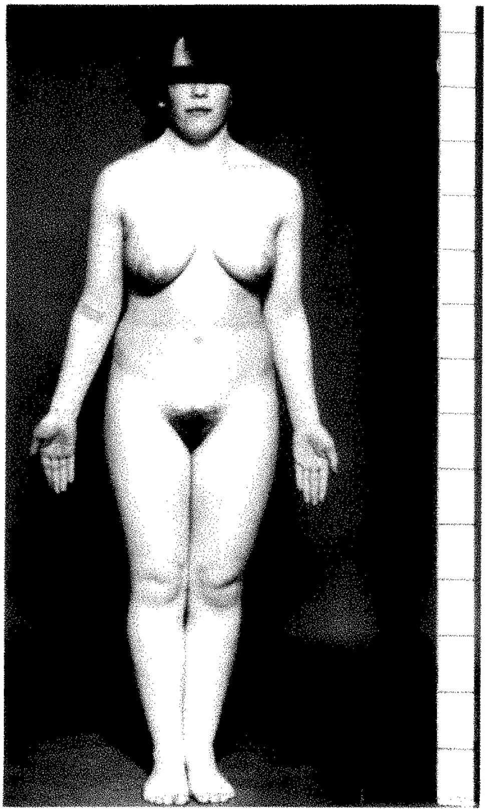

Fig. 1. Patient with 45 X Turner's syndrome, aged 13·6 years, showing short stature, neck webbing, cubitus valgus and 2° sexual maturation—Tanner stage 5.

while the younger sister was prepubertal (Tanner breast stage 0) and asymptomatic (Fig. 4).

Methods

Transabdominal pelvic scans were all performed by a single observer (J.A.), using an Aloka real-time sector scanner equipped with a 3·5-mHz long-focused transducer. Ovaries were identified and measured in three planes; the volume was calculated assuming the shape to be that of a prolate ellipse (Adams *et al.* 1985). Polycystic ovaries were identified using published criteria (Adams *et al.* 1985).

Steroid, thyroid hormone, and gonadotrophin assays, together with autoantibody studies, were performed in the routine laboratories of the Middlesex Hospital using standard in-house radioimmunoassays and serology.

Blood from the patient and her parents was drawn into tubes containing EDTA and stored at −70°C. On thawing, the cells were lysed and the DNA extracted into phenol, enzymatically digested with a series of restriction endonucleases, and the fragments hybridized with a number of DNA probes directed at the X chromosome. Autoradiography was performed after gel electrophoresis.

High-resolution karyotyping was performed in the Prince Philip Research Laboratories, Guy's Hospital Medical School, under the direction of Professor Martin Bobrow, on lymphocytes cultured after stimulation with phytohaemagglutinin.

Results

Table 2 shows the dimensions of ovaries and uteri of the family in comparison with normal women and women with polycystic ovaries (Hague 1988), in addition to data from 12 adult patients with Turner's syndrome (45 X—4, 45 X/46 XXq—1, 46 XXq—1, 46 XiX—1, 45 X/46 XX—1, 45 X/46 XiX—1, 45 X/46 XsX—1, 45 X/46 i(Xq)—1, 45 X/47 XXX—1) attending the reproductive endocrine clinic at the Middlesex Hospital (unpublished data).

The endocrine profile of the prepubertal sibling showed serum LH 0·9 U/l, FSH 0·3 U/l, testosterone 0·9 U/l, oestradiol 154 pmol/l, prolactin 102 mU/l.

High resolution banding studies of both the patient's and her mother's lymphocyte karyotype confirmed the lack of mosaicism and

Table 1. Laboratory findings in a girl with Turner's syndrome

Investigation	Finding
Karyotype	45 X in all 10 cells counted
Buccal smear	No Barr bodies seen in 200 cells
Serum	
LH	6·3 U/l
FSH	4·0 U/l
Oestradiol	300 pmol/l
Progesterone	7·0 nmol/l
Testosterone	1·7 nmol/l
Thyroxine	88 nmol/l
TSH	3·9 U/l
Autoantibodies	None detected (thyroid, gastric, pancreas)
Pelvic ultrasound (Figs 2 & 3)	Uterus 87×37 mm Endometrium 18 mm Left ovary 38×33 mm cyst Right ovary 38×30×14 mm polycystic pattern

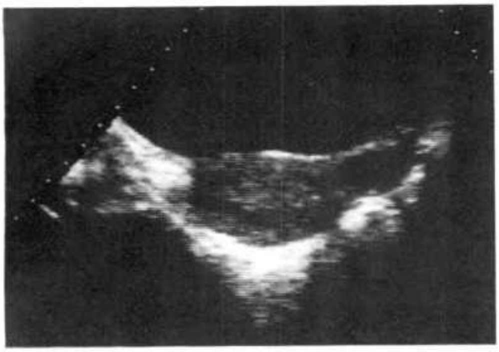

Fig. 2. Longitudinal scan through pelvis before therapy, showing uterus with markedly thickened endometrium (18 mm) (1 cm markers).

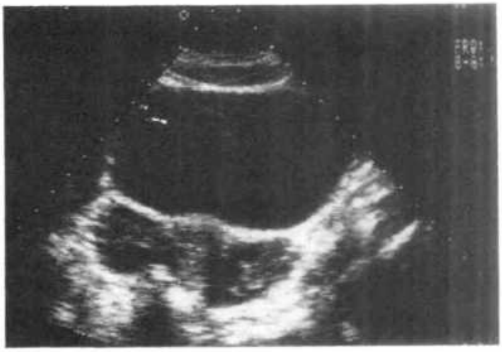

Fig. 3. Transverse scan through pelvis showing bladder, uterus and enlarged ovaries with peripheral follicles and dense central stroma (1 cm markers).

failed to reveal any evidence of translocation of chromosomal material.

Eight polymorphic DNA probes were used to identify the parental origin of the single X chromosome of the patient as maternal (Fig. 5).

Discussion

This case raises in the first instance the question of ascertainment of polycystic ovaries using high-resolution pelvic ultrasonography: does this girl with Turner's syndrome, and, indeed, does her younger prepubertal asymptomatic sister, have polycystic ovaries? Comparison of their ultrasonically detected ovarian volumes with those of (a) women with normal ovaries, (b) women with symptomatic polycystic ovaries, and (c) 12 adult women with Turner's syndrome (Table 2) shows that the ovarian volumes of the patient and her mother fall more than 2 SD above the mean of the ovarian volumes of the women with normal ovaries, are more than 10 times the mean ovarian volume from the women with Turner's syndrome, and fall within the range of the volumes found in the women with symptomatic polycystic ovaries. The pattern of follicle distribution and of ovarian stroma seen in all four family members is characteristic of that seen in women with polycystic ovary syndrome (Adams *et al.* 1985). Furthermore, the degree of endometrial thickening seen in the patient is greater than that usually found in the follicular phase of the normal menstrual cycle (Adams *et al.* 1988), indicating that the ovaries have functioning endocrine tissue. The persistence of the polycystic changes in both the patient and her elder sibling, despite gonadotrophin suppression with the oral contraceptive pill, is further evidence for a primary ovarian lesion, in contrast to the gonadotrophin-dependent multifollicular changes seen in peripubertal girls (Stanhope *et al.* 1985). Finally, the presence of a polycystic morphology in the ovaries of the prepubertal sister (Fig. 4) again suggests a familial primary lesion in the ovary.

The diagnosis of Turner's syndrome in this patient is in no doubt, with the classical findings of short stature, cubitus valgus, pterygium collis and typical facies, although some would classify her as having the Ullrich syndrome (Ullrich 1930) in view of the normal secondary sexual characteristics (Fig. 1). The 45 X leucocyte karyotype is matched by the absence of Barr bodies from the buccal squames. Further tissues, in particular the ovaries, have not been karyotyped, but Kemmann *et al.* (1977) point out that, of 23 women in whom gonadal

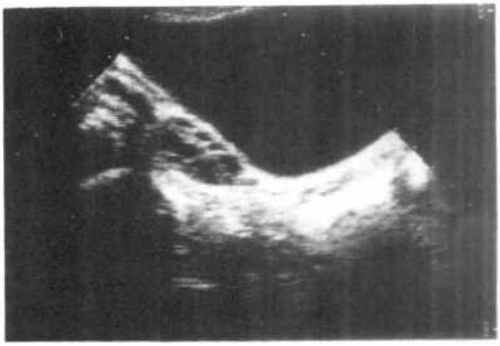

Fig. 4. Transverse scan through pelvis of patient's younger sister (aged 6 years) showing ovarian morphology indistinguishable from that found in women with polycystic ovary syndrome (1 cm markers).

Table 2. Pelvic ultrasound data

	Ovarian volume (ml)		Uterine area (cm^2)	
	Mean	(SD)	Mean	(SD)
Normal adult ($n=185$)	5·4	0·4	23·0	1·0
Polycystic ovary syndrome ($n=63$)	10·0	1·1	24·1	1·4
Turner's syndrome ($n=12$)	0·5	0·45	8·0	4·59
Patient (13·6 years)	10·8		38·5	
Mother	12·6		(Hysterectomy)	
Older sister (18 years)*	5·4		27·9	
Younger sister (6 years)	3·3		3·2	

*The older sister was taking oral contraceptives.

karyotype was compared with leucocyte karyotype, only one showed a discrepancy (while it is also of interest that they had one 45 X patient with regular menses). The chances that this patient has a mosaicism are therefore small.

The aetiology of polycystic ovaries remains a cause for debate, hypotheses ranging from a hypothalamic disturbance of gonadotrophin secretion (Yen *et al.* 1970), through a result of abnormal secretion of adrenal androgens (Lobo 1984), to a primary ovarian lesion (Erickson *et al.* 1979). Familial cases of polycystic ovary syndrome have been reported (Cooper *et al.* 1964; Wilroy *et al.* 1975; Ferriman & Purdie 1979), but the mode of transmission has not been established, at least in part because of the difficulty of identifying the phenotype—the symptoms being very variable. We have previously presented data from 67 pedigrees, using the morphology of ultrasonically detected polycystic ovaries as a phenotype, that have shown a much higher familial prevalence than previously recognized together with segregation ratios that do not fit Mendelian patterns of inheritance (Hague *et al.* 1988).

A number of reports in the literature describe an association between polycystic ovaries or polycystic ovary syndrome and chromosomal abnormalities. There have been three reports of women with phenotypic Turner's syndrome (short stature, cubitus valgus, pterygium collis) and associated polycystic ovaries (Williams *et al.* 1969; Zarate *et al.* 1969; Givens *et al.* 1975). Of the six patients described, five had histological evidence and one had laparoscopic evidence of polycystic ovaries. Only one of these (Zarate *et al.* 1969) had a 45 X karyotype, while one of the others (Givens *et al.* 1975) had a 45 X/46 XX mosaic karyotype. The remainder were 46 XX.

Other authors have described patients with polycystic ovaries who have also had karyotypic abnormalities but without the Turner phenotype (Netter *et al.* 1961; Gardo *et al.* 1974; Parker *et al.* 1980). The abnormalities noted were X chromosome mosaicism (13 cases) and pseudodiploidy with trisomy 14 (5 of 15 patients studied). One report has described two siblings of whom one had 45 X/46 XXr Turner's syndrome and the other polycystic ovary syndrome (46 XX) (Tuncbilek & Say 1971). A further report described a family with polycystic ovary syndrome in which mother and two daughters had an increased frequency of tetraploidy in cultured lymphocytes, one daughter also having an increased frequency of tetraploidy in cultured fibroblasts (Rojanasakul *et al.* 1985).

Macroscopic and histological changes compatible with polycystic ovaries have been described in two of nine 46 XX women with secondary amenorrhoea and premature ovarian failure with elevated gonadotrophin excretion (Kinch *et al.* 1963). The appearances were attributed to a 'running down ovary'. Our group has documented ultrasonically detected polycystic ovaries in three of 70 (46 XX) women with hypergonadotrophic secondary amenorrhoea, one of whom had the morphology confirmed by laparoscopic biopsy; one other woman developed the ultrasound appearance of polycystic

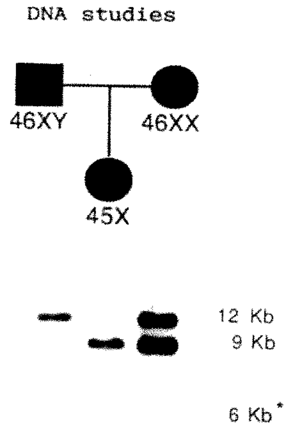

Fig. 5. Autoradiograph of genomic DNA hybridized with probe L1.28 from Xp21 region. Taq 1 digested genomic DNA reveals two alleles (12 KB, 9 Kb). The 6 Kb fragment* results from a previous hybridization which was uninformative.

ovaries when menses and ovulatory activity recommenced (unpublished data). If the ultrasound appearances in the 45 X patient described here had been confined to the patient alone, it would perhaps be possible that her ovaries were also 'running down'. Since, however, the polycystic pattern was also seen in the other family members of this patient, none of whom had evidence of ovarian failure or karyotype abnormality, it seems more likely that her polycystic ovaries were familial in the same way as those described earlier (Hague *et al* 1988).

Givens *et al.* (1975) used their data of women with Turner's syndrome and polycystic ovaries in support of their hypothesis that polycystic ovary syndrome may be X-linked. The present family provided an opportunity to test this hypothesis. Both the mother and the elder sister had had dysfunctional uterine bleeding, a symptom compatible with polycystic ovary syndrome, such that the mother had required hysterectomy and the elder sister needed cycle control with the oral contraceptive pill; mother had also had one miscarriage and a period of secondary infertility. The younger sister had no symptoms but had ovarian morphology indistinguishable from that of women with polycystic ovary syndrome (Fig. 4). The possibility that the patient's single X chromosome might be paternal, which would tend to exclude X-linkage, was then examined. The demonstration that the X chromosome of the patient matched one of the maternal X chromosomes and not the paternal X leaves Givens' hypothesis untested.

The possibility of fertility in this girl has been raised as a question by her parents. Menses and fertility are occasionally seen in women with Turner's syndrome associated with 45 X karyotype (Dewhurst 1978; Baudier *et al.* 1985). Although a high rate of genetic abnormality has been described for the offspring of such women, it has been pointed out (Dewhurst 1978) that assessment of the rate is biased by the mode of ascertainment of the maternal karyotype, such that those women found to have an abnormal karyotype following detection of a fetal abnormality have a much worse reproductive performance than the women whose karyotype is already known. The options open to this patient will now include oocyte harvest and storage with a view to subsequent in-vitro fertilization and embryo transfer.

Analysis of large amounts of data for human autosomal trisomy has revealed that more than 70% of the errors arise at the first meiotic division (Ishikiriyama & Niikawa 1984). One hypothesis is that these errors may be due to abnormal segregation and pairing (Jongbloet & Vrieze 1985). Human oocytes begin to enter meiosis at 8 to 10 weeks of fetal life, a time when the ovary begins oestrogen synthesis and the adrenal begins steroid biosynthesis (Villee 1969). The process of meiosis is held in the 'resting' dictyotene stage by the putative oocyte maturation inhibitor (OMI) (Tsafifri & Channing 1975), and completion of meiosis is largely dependent on the surge of luteinizing hormone (LH) preceding ovulation (Channing *et al.* 1982). Secretion of LH is known to be abnormal in many patients with polycystic ovaries (Yen *et al.* 1970). This abnormal secretion may perhaps contribute to the disorder of meiosis at the X chromosome and might thus be responsible, at least in part, for the increased rate of miscarriage seen in many patients with polycystic ovaries (Homburg *et al.* 1988).

In conclusion, the patient presented here is the second recorded case of 45 X Turner's syndrome with morphological evidence of polycystic ovaries and the first in which the polycystic pattern has also been shown in the karyotypically normal mother and sisters. X-linked inheritance for familial polycystic ovaries has not been excluded. The presence of functional ovaries, let alone polycystic ovaries, in the absence of one X chromosome remains a baffling phenomenon which requires further elucidation. Further information may be forthcoming if the patient undergoes oocyte harvest with a view to enhancing her fertility. Perhaps polycystic ovaries are an inheritable form of mild ovarian dysgenesis.

Acknowledgments

We are grateful to Dr P Magill (Hoechst UK), for the Aloka scanner, and to Professor Martin Bobrow for the high-resolution karyotyping.

W.M.H. is a Frances and Augustus Newman research fellow.

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SHORT COMMUNICATIONS

Measuring low-grade albuminuria in pregnancy

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The immunoassay of albumin for detection of elevated micro albuminuria is a well-proven diagnostic tool in early kidney disease or damage in the diabetic patient (Mogensen 1987). The circadian rhythm of albumin excretion makes it preferable to use 24-h urine samples (Koopman *et al.* 1985), which limits the practical use of the determination. For pregnancy we are aware of only a single study using this assay in 24-h urine samples (Lopez Espinoza *et al.* 1986) and a few reports based on a more useful single voided urine sample with (Wright *et al.* 1987) or without (Rodriguez *et al.* 1988) some correction to estimate the 24-h excretion. These corrections, well established in the case of proteinuria (Uttendorfsky *et al.* 1988), cannot be extended automatically to the micro albuminuria range. Moreover, albumin is only one of the components of total urine protein. As far as we know, there is no convincing study that shows whether the albumin concentration or the albumin/creatinine ratio from a single voided urine sample can be used to measure 24-h low-grade albuminuria. Low-grade albuminuria is defined as albuminuria of ≤100 mg in a 24-h period.

We investigated a group of 38 patients in the third trimester of pregnancy. All were in-patients in our high-risk pregnancy department for a variety of reasons and all had low-grade albuminuria. The albumin concentration and the albumin/creatinine ratio of a single sample of urine were determined and compared with the corresponding 24-h albumin excretion.

Patients were asked to collect urine for 24 h, starting at midnight. During these 24 h one single voided late morning sample was collected separately. Concentration of creatinine was measured by a standard clinical chemical method, and albumin in urine was determined by the use of a centrifugal analyser as described by Koomen *et al.* (1986). The inter-run coefficient of variation for albumin in urine was less than 5%.

The normal excretion in our patient group was estimated to be ≤25 mg in 24 h (Mogensen 1987). Both the single voided sample albumin concentration (mg/l, $Y1$) and the albumin/creatinine ratio (mg/mmol, $Y2$) correlated well with the 24-h albumin excretion (mg/24 h, X). The equations are $Y1 = 1{\cdot}26X - 4$; $N = 38$; $r = 0{\cdot}82$; and $Y2 = 0{\cdot}11X - 0{\cdot}12$; $N = 37$ (in one sample no creatinine value was available); $r = 0{\cdot}86$. The contingency Table 1 shows that both the single sample albumin concentration and single sample albumin/creatinine ratio discriminate well between normal and slightly elevated 24-h albumin excretion. This indicates that increases in 24-h albumin excretion from normal to slightly elevated values can be predicted reasonably well from a single voided late morning urine sample In the third trimester of pregnancy the creatinine excretion decreases fractionally (Davison *et al.* 1980). This change has to be taken into account using the albumin/creatinine ratio for longitudinal studies.

We conclude that, especially with outpatients, the more practical estimate of albumin concentration and albumin/creatinine ratio in a single voided urine sample can be used to study early kidney involvement in hypertensive and other medical disorders during pregnancy.

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Table 1. Contingency table

Single voided urine sample	24-h albumin excretion (mg)		Predictive value
Albumin contraction* (mg/l)	≤25	>25	Sensitivity 75% Specificity 100%
≤27	30	2	
>27	0	6	
Albumin–creatinine ratio* (mg/mmol)			Sensitivity 75% Specificity 100%
≤2·6	29	2	
>2·6	0	6	

*The corresponding cut-off points were computed with the help of the correlation equations

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A randomized double-blind controlled trial of the value of diethylstilboestrol therapy in pregnancy: 35-year follow-up of mothers and their offspring

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In 1983 we reported a long-term follow-up of 650 women and their offspring who had taken part in a trial of diethylstilboestrol (DES) during pregnancy (Vessey *et al.* 1983). We found no harmful effect of DES exposure in the mothers. Amongst the exposed daughters there was an excess of minor benign cervical lesions, unfavourable pregnancy outcomes and psychiatric illnesses. None of the daughters had developed clear-cell carcinomas. There was also an excess of psychiatric illnesses in exposed sons, while one had died from a testicular teratoma.

Since our last report we have continued to monitor deaths and cancer registrations occurring amongst the trial participants. We report the latest findings here.

Subjects and methods

The methods have been described in our earlier paper (Vessey *et al.* 1983). The women were admitted to the trial from March 1952 until March 1953. Half received DES and half received placebo. DES was started as soon after the 6th week of pregnancy as possible and the mean dose ingested was 11·5 g. Deaths and cancer registrations have been notified to us by the National Health Service Central Registry at Southport.

Table 1. Deaths and cancers occurring among 590 mothers who received diethylstilboestrol or placebo treatment during pregnancy

	Deaths					
	DES group (n = 292)			Placebo group (n = 298)		
Cause of death	A	B	Total	A	B	Total
Breast cancer	2	1	3	4	2	6
Ovarian cancer	0	1	1	0	1	1
Colon cancer	0	1	1	2	3	5
Glioma	1	0	1	1	2	3
Other cancer	3	1	4	2	0	2
All cancers	6	4	10*	9	8	17
Other causes	5	6	11	9	6	15
Total deaths	11	10	21**	18	14	32

Relative risks (and 95% confidence intervals) of death in DES group compared with controls:
*Cancer deaths RR = 0·59 (0·27–1·32)
**All deaths RR = 0·67 (0·38–1·19)

	Reproductive cancer incidence, deaths and registrations					
	DES group (n = 292)			Placebo group (n = 298)		
Type of tumour	C	D	Total	C	D	Total
Breast cancer	9	1	10	10	0	10
Cervix cancer	2	1	3	4	0	4
Endometrial cancer	0	0	0	2	0	2
Ovarian cancer	2	0	2	0	1	1
Total reproductive cancers	13	2	15***	16	1	17

Relative risk and 95% confidence interval of reproductive cancer in DES group compared with controls:
*** RR = 0·90 (0·44–1·84).

A = Deaths registered up to 1 January 1977 (reported previously by Vessey *et al.* (1983)
B = Subsequent deaths.
C = Reproductive cancer incidence (deaths, registrations, data from GP questionnaires up to 1983, reported previously by Vessey *et al.* (1983).
D = Subsequent reproductive cancer registrations and deaths.

Results

The data presented include deaths and new cancers identified from the time we prepared our last report up to 31 May 1988. The denominators take account of embarkations and cancelled registrations reported previously.

Mothers

Table 1 shows the causes of death of the mothers who have died and the incidence of reproductive cancer (fatal and non-fatal). There are no significant differences between the treatment groups. The occurrence of four deaths from glioma (only one in the DES group) is remarkable; less than one would have been expected.

Daughters

Only one daughter has died since the previous results were published. There have now been two deaths after the second year of life, one in each treatment group, both from multiple trauma.

Four cancers have been notified amongst the daughters: two in the placebo group (both CIN) and two in the DES group (one CIN and one carcinoma of the colon). There have been no cases of clear-cell carcinoma.

Sons

Nine liveborn sons have died, five in the placebo group and four in the DES group. Seven of these deaths were reported in 1983. Of the two new deaths, one occurred in each group (cerebrovascular accident, placebo group; multiple injuries, DES group). No new cancers have been notified.

Discussion

These results do not alter our previous conclusions. In particular, they offer no support to the finding of an increased rate of breast cancer amongst DES-exposed mothers (Bibbo *et al.* 1978; Beral & Colwell 1980). Our data are also reassuring about cancer risk at other sites. We have no explanation for the fact that four women have died from glioma, but note that only one of these was in the DES group.

We have found no clear-cell carcinomas amongst the daughters. This is not surprising as the best current estimate of the risk amongst those exposed to DES *in utero* is only about 1 in 1000 from birth to age 34 (Melnick *et al.* 1987). Of the reported cases of clear-cell cancer 91% have occurred before the age of 27, so we would not expect to find new cases now (Melnick *et al.* 1987). The excess of benign cervical abnormalities in the exposed daughters reported by Vessey *et al.* (1983) has not led to an increased rate of cervical cancer in these women so far.

We noted a fatal case of teratoma of the testis occurring in an exposed son in the last report. No further cases have occurred, but on balance the published evidence supports a link between 'hormone' exposure *in utero* (not specifically DES) and the risk of testicular cancer (Henderson *et al.* 1988).

In conclusion, our data on the long-term effects of DES exposure *in utero* are still reassuring. As the mothers and their offspring get older and their death rates rise, we will be able to obtain more data on cancer risks and causes of death.

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CORRESPONDENCE

Successful pregnancy after selective embolization of a post-molar vascular malformation

Dear Sir,

We were very interested to read the article by Tacchi & Loose [*Br J Obstet Gynaecol* (1988) **95,** 814–817] reporting the successful treatment of a massive uterine haemorrhage due to post-molar arteriovenous malformations, using selective embolization of the afferent arteries.

In the discussion the authors stress that their case is the first report of a successful pregnancy following embolization for this condition.

May we remind you that we have previously reported a successful embolization of a gross congenital arteriovenous uterine malformation which caused life-threatening episodes of haemorrhage in a 25-year-old woman (Wilms *et al.* 1986). After this procedure her normal menstrual cycle was restored, she conceived readily and gave birth to a normal healthy baby after an uneventful pregnancy (Poppe *et al.* 1987).

Apart from the congenital nature of the arteriovenous malformation in our patient, therapy and post-treatment evolution was not different from that described by Tacchi & Loose. To the best of our knowledge the report in this Journal is the fourth published case of a successful pregnancy of a uterine vascular malformation.

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Book review by Geoffrey Chamberlain. The Obstetric Forceps: A Short History and Descriptive Catalogue of the Forceps in the Museum of the Royal College of Obstetricians and Gynaecologists

Dear Sir,

I was pleased to see Professor Chamberlain's review of my book on the obstetric forceps [*Br J Obstet Gynaecol* (1989) **96,** 125]. He mentioned the desirability of slide sets and I would just like to draw your attention to the fact that the first set of six slides and explanatory notes in a plastic wallet, which deals with the Chamberlen instruments, has been available for about 9 months from the Royal College of Obstetricians and Gynaecologists, price £3.00.

All the other forceps have been photographed in colour and black and white and individual copies can be made to order.

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Malignant lymphoma presenting as initial symptom in the uterus

Dear Sir,

Maeda *et al.* [*Br J Obstet Gynaecol* (1988) **95,** 1195–1197] report a patient with malignant lymphoma who presented with uterine bleeding. Although non-Hodgkin's lymphoma, diffuse, large-cell type is classified as intermediate grade malignancy by The Non-Hodgkin's Lymphoma Pathological Classification Project (1982), the authors rightly point out that its median survival time of 1·5 years is almost equivalent to that of immunoblastic type (1·3 years) or lymphoblastic type (2·0 years) in high-grade malignancy.

Malignant lymphoma, diffuse, large-cell type, is synonymous with the diffuse histiocytic lymphoma as classified by Rappaport (1966) and as such should be considered an aggressive lymphoma. The clinical course, especially with advanced presentations, is characterized by rapid progression and early mortality except in patients treated aggressively when a proportion may be cured (Horwich 1988).

Optimal management can only be achieved after adequate staging. Extranodal presentation occurs in approximately 40% of patients with non-Hodgkin's lymphoma. Dissemination is often widespread. Bone marrow involvement is present in 19% of diffuse histiocytic lymphomas (Mckelvey *et al.* 1976).

Staging investigations should therefore consist of a minimum of full blood count, plasma viscosity, biochemical profile, chest X-ray, CT scan of chest and abdomen, and bone marrow aspiration and trephine.

The role of gallium-67 scanning in the staging of malignant lymphoma is debatable and remains subject to continuous review. In non-Hodgkin's lymphoma histological cell type has a strong correlation with sensitivity. Whilst sensitivity is only 50% in lymphocytic or mixed lymphocytic and histiocytic lymphoma, this rises to 70–89% for histiocytic lymphomas (Hoffer 1980; Andrews *et al.* 1978).

Multiple lymph node biopsies are sometimes necessary as reactive hyperplasia may be detected in lymph nodes adjacent to an involved node (Epenetos 1988).

The patient reported by Maeda *et al.* (1988) was inadequately staged, and in spite of a gallium-67 scan showing several hot nodules in the pelvic cavity and other sites suggestive of disseminated disease, chemotherapy was considered unnecessary.

Advanced disease requires aggressive chemotherapy for control. With increasing skill in the use of chemotherapy combinations a young, otherwise fit, patient with advanced aggressive non-Hodgkin's lymphoma has a 70–80% chance of complete remission and probably greater than 50% chance of being cured (Horwich 1988).

Malignant lymphoma demands accurate diagnosis, staging and treatment, best carried out in specialist oncology centres by those practised in its management.

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Authors' reply

Dear Sir,

I thank Dr Divers for his comments on our paper. In our case, although a scintigram using ^{67}Ga just before the hysterectomy showed a hot nodule at the bottom of the pelvic cavity, careful histological examination failed to demonstrate any residual malignant lymphoma in the uterus or regional lymph nodes. Several other hot nodules were detected in the epiphyseal regions of the shoulder and hip joints. Enlargement of lymph nodes was not detected until leukaemic changes developed in the terminal stage of the disease. Gallium citrate is known to concentrate in epiphyses of long bones in normal individuals, and is used to detect areas of inflammation (Harbert & Gonçalves da Rocha 1984). We thought the hot nodule in the pelvic cavity to be an inflammatory focus, and those near the joints to be a physiological accumulation of ^{67}Ga in the epiphyses. In retrospect, our patient seems to have been somewhat inadequately staged. However, because of the problems of interpretation described above, it was not possible to detect that the disease was so advanced at the time of the hysterectomy, and, consequently, aggressive chemotherapy was not arranged.

However, this case has taught us a valuable lesson and we hope this will also be true for your readers.

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Reference

Harbert J. & Gonçalves da Rocha A. F. (1984) *Textbook of Nuclear Medicine Vol. II. Clinical Applications*, 2nd edn Lea & Febiger, Philadelphia, pp 639-662.

Is routine antenatal booking vaginal examination necessary for reasons other than cervical cytology if ultrasound examination is planned

Dear Sir,

The article by Dr O'Donovan *et al.* [*Br J Obstet Gynaecol* (1988) **95**, 556–559] on routine vaginal examination at booking did not leave much confidence in the value of such practice. The wide variation in the use of vaginal examinations in the European region was recently shown in a survey of current policies in university hospitals in EC countries (Huisjes *et al.* 1988). We are able to give additional information on the use of vaginal examinations (digital with or without speculum) in antenatal care outside hospitals in Denmark.

The national antenatal care programme in Denmark is shared between general practitioners (GPs), centres of midwifery, and hospital outpatient clinics (OPCs). Women will follow a scheme including three visits to the GP, who has the woman on his/her list, a minimum of five visits to a midwife, and at least one visit to the OPC (in week 16–20).

In the winter of 1986/87 we conducted a national survey of the content of antenatal consultations on the basis of questionnaires to care providers. In the non-hospital part of the study, all midwives who gave antenatal care (n = 678) and a randomly selected third of GPs in the country (n =957) were asked to complete one questionnaire after a specified consultation. Overall, 75% of the GPs and 89% of the midwives returned the questionnaires of which 593 (62%) were complete from GPs and 584 (86%) were complete from midwives.

Table 1. Frequencies of vaginal examinations (digital with or without speculum) at antenatal check-ups outside hospital departments in Denmark

Consultation type	General practitioner	Midwife
First visit	307/352 (92·9%)	30/109 (27·5%)
Follow-up visit		
<33 weeks	39/117 (33·3%)	45/134 (33·6%)
≥33 weeks	62/120 (51·4%)	115/306 (37·6%)
Data missing	4	35

Table 1 shows frequencies of vaginal examination in first and follow-up antenatal visits to GPs and midwives.

Vaginal examinations are officially recommended by the National Board of Health at each of the three routine visits to the GP (Sundhedsstyrelsen 1985). The data indicate that vaginal examinations are not routine in antenatal check-ups outside hospital in Denmark. However, GPs will normally do a vaginal examination at the first antenatal visit and many GPs and midwives do indeed make these examinations as a part of antenatal check-ups later in pregnancy as well.

Efficacy and possible secondary effects of these examinations are still not fully documented, but useful information may result from ongoing research such as the multinational randomized controlled trial referred to by Blondel *et al.* (1988).

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References

Blondel B., Le Coutour X , Kaminski M. & Buekens P. (1988) Routine antenatal vaginal examinations (letter). *Lancet* **ii**, 846-847

Huisjes H. J., Buekens P. & Reid M (eds) (1988) Antenatal screening. Current policies in the EC and evaluation *Eur J Gynecol Reprod Biol* **Suppl 28.**

O'Donovan P., Gupta J., Savage J., Thornton J. G & Lilford J. (1988) Is routine antenatal booking vaginal examination necessary for reasons other than cervical cytology if ultrasound examination is planned? *Br J Obstet Gynaecol* **95**, 556-559.

Sundhedsstyrelsen (1985) *Retningslinjer for Svangerskabshygiejne og Fodselshjælp.* Kobenhavn

Authors' reply

Dear Sir,

We agree that the multinational randomized trial may provide useful information. It should be fully realized, however, that the anticipated negative results will not mean anything clinically. They will certainly not mean that vaginal examination should be abandoned, because even this multinational trial will not be nearly large enough to detect the magnitude of treatment effect, which patients consider sufficient to warrant the discomfort of pelvic examination.

We conducted a series of certainty equivalence multiple gambles which showed that people would be prepared to put up with the discomfort of vaginal examination for a 1 in 1000 reduction in the risk of fetal loss or ovarian cancer. Randomization of 250 000 women would be required to have even an 80% chance of showing a reduction in perinatal mortality from 9 to 8/1000. This decision-theory approach to the design of randomized trials emphasizes the limited contribution that this method can make to many obstetric controversies.

We do not think that routine vaginal examination is warranted, but we also do not think that a randomized trial can solve this issue.

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BOOK REVIEWS

Diagnostic Cytopathology: A Text and Colour Atlas by Chandra Grubb. Churchill Livingstone, Edinburgh, 1988, 244 pages with 640 illustrations, £29.50

This text and atlas is of a quality that we have come to expect from Dr Chandra Grubb and her publisher, Churchill Livingstone. Indeed the illustrations are so superb that the length and breadth of the cytological world must have been searched to find them. If I have a criticism, it is that they are too good—certainly of a quality all too rarely encountered in routine cytological practice, giving the impression that what is often a difficult business is in fact akin to child's play. No such luck, of course, as the problem areas always seem to occur in badly prepared specimens and interpretation is difficult. No such problem here, in this highly recommended book, which must be on every cytology laboratory's shelves. What this reviewer would really like to see on the shelf is a 'Textbook of Bad Cytology' illustrating the multifarious problems so frequently encountered in interpreting calamitously bad material. How about it, Churchill Livingstone?

Robert Yule

Endometriosis (Contributions to Gynecology and Obstetrics Vol.16) Proceedings of the International Meeting on Endometriosis, Clermont-Ferrand, 1986 edited by M. A. Bruhat & M. Canis. Karger, Basel, 1987, 394 pages with figures and tables, £104.00

This multi-author book is the result of an international symposium on endometriosis held at Clermont-Ferrand in November 1986. There are chapters on the aetiology, pathophysiology, classification, diagnosis, infertility treatment and management. The book introduces, for me, some entirely new concepts such as asymptomatic bacteriospermia and new words which have not yet reached me, such as dysovulation. Many of the chapters are badly written or certainly badly translated with many of the authors' views entirely based on conjectural and repetitive opinions. Some references are inaccurate.

The number of actual controlled clinical studies is limited, and (on page 215) the question 'Why are there so few trials in human reproduction?' has my utmost support. There are a few useful signposts concerning future management such as Sutton on the CO_2 laser and (on page 151) the free communications of Thomas and Cooke.

However, the bulk of this book is repetitive and poorly edited and at £104 for nearly 400 pages should only be held for historical interest in major gynaecological libraries.

John McGarry

Biopsy Pathology and Cytology of the Cervix by D. V. Coleman & D. M. D. Evans. Chapman & Hall, London, 1988, 396 pages with figures and tables, £48.50

The authors of this book are very experienced in the field of cervical pathology, and the depth of understanding of their subject is shown by the deceptively simple way in which this book is written and presented. It covers the principles of cytological and histological methods, the features of the normal cervix, non-neoplastic disease of the cervix and intraepithelial and invasive neoplasia.

It is an excellent book, well written, beautifully illustrated, and successfully combines the histology and cytology of cervical disease in an appropriate and functionally useful way. The authors use the nomenclature which is recommended by the BSCC and endorsed by the Intercollegiate Working Party on Cervical Cytology and therefore it meets the recommendations upon which current training is based.

To point out any minor defects seems almost churlish but it is a pity that the authors did not expand their discussion on microinvasive tumours to include the volumetric measurement of the invasive component, a technique increasingly used in many laboratories, and why did they reproduce the very poor illustrations of glassy cell tumour?

These trivial matters can, however, be ignored and I am sure that this text will become essential reading, not only for those training in colposcopy and pathology but for the established specialist who will still find need to refer to the book. I think it should be found in the library of everyone involved in the management of cervical neoplasia. I hope they enjoy reading it as much as I did.

C. H. Buckley

Gynaecological Endoscopy by Alan G. Gordon & Victor B. Lewis. Chapman & Hall, London, 1988, fully illustrated with colour plates, £45.00

Laparoscopy is one of the commonest gynaecological operations performed in this country and its introduction was largely due to the efforts of one man, the late Patrick Steptoe, working from a district general hospital in Oldham. It is therefore entirely appropriate that he should have been asked to write the forward of this excellent work by Alan Gordon of Hull and Victor Lewis of Watford, both of whom have amassed a wealth of endoscopic experience in the hurly-burly of busy general hospital life.

Professor Hans Frangenheim who, along with Palmer of Paris, is usually considered as the father of modern laparoscopy, has written a fascinating history of the subject in the first chapter. We tend to think of this revolutionary concept of being able to visualize the pelvic organs without major surgery as a development of the last three decades but, in reality, it has been around much longer than that. Even before Edison invented the electric light bulb attempts were made in 1806 to look inside the body using reflected light from candles, and the first laparoscopies using a pneumoperitoneum were performed as long ago as 1912 by Jacobaeus. Since then it has had its ups and downs in popularity, even being replaced for a while in the 1940s by culdoscopy, and this book is an excellent introduction to the new era of operative laparoscopy.

The book provides a comprehensive and highly practical introduction to the techniques of laparoscopy and hysteroscopy with helpful tips for anyone starting to work in this field and also for their anaesthetists. The hazards and complications of laparoscopy are quite properly stressed, but I do not feel sufficient attention has been drawn to the dangers of hysteroscopy, particularly gas embolism, and this is particularly important because the hysteroscope is only just starting to be used in this country, whereas laparoscopy is already firmly established. Although most of the book deals with the laparoscopic diagnosis of infertility, pelvic infection and endometriosis, there are excellent chapters on laparoscopic surgery as well as the newer techniques of salpingoscopy, chorionoscopy and in-vitro fertilization. Although I always cringe when I see the introduction of strange new words into the English language—such as 'pelviscopy' and 'morcellement'—I have to admire the skill of Professor Semm's techniques and the brilliant quality of his photographs.

Each page of the book is illustrated by excellent photographs taken through the laparoscope and beside each one is an anatomical sketch, carefully labelled so that the reader can identify the structures Alan Gordon and Victor Lewis have managed to persuade many specialists in the world of endoscopy from seven European countries to supply an extensive range of photographs from their collections, as well as some excellent sequences of operative surgery through the laparoscope and hysteroscope. Some of the photographs are really quite illuminating. The fact that hyperstimulation of the ovary looked so similar to carcinoma of the ovary and the adhesions which one sees around the liver, and can divide laparoscopically, providing dramatic pain relief, was a new eponymous syndrome for me—the Fitzhugh-Curtis syndrome.

Operating laparoscopy and hysteroscopy is such a fast-growing field that I would have welcomed a few more sequences of laser laparoscopy and hysteroscopy, as well as some of the more advanced operative laparoscopy techniques that are used for the treatment of severe endometriosis, but possibly these could be a feature of future editions. My other slight reservation concerns the inclusion of a section on culdoscopy which, although beautifully illustrated and documented from Professor James Scott's department, seems to offer little advantage over conventional laparoscopy and the considerable disadvantage of having always to operate through a questionably sterile field.

The authors and publishers are to be congratulated for producing a book, lavishly illustrated with 370 colour photographs, at such a reasonable price. This excellent guide should be in the possession of all gynaecological endoscopists and should be on the bookshelves of every gynaecological theatre throughout the land.

Chris Sutton

Medical Counselling Before Pregnancy by Dorothy Reycroft Hollingsworth & Robert Resnik. Churchill Livingstone, New York, Edinburgh, 1988, 551 pages with figures and tables, £50.00

This is a comprehensive book aiming to provide information on a wide variety of problems and diseases which have a bearing on the management of, and even the advisability of, a pregnancy. Although the title correctly implies that these matters are best gone into before the pregnancy, in real life the book is likely to be referred to as often during pregnancy.

The initial section covers general topics such as maternal age, diet, work and lifestyle. Genetic counselling occupies the second section. It includes a chapter on basic inheritance, one on prenatal diagnostic techniques, and a somewhat incongruous one on dermatological genetics.

It is the third section of the book which provides the most valuable information. There are 12 chapters, each an in-depth review of a specific medical condition. The impact of pregnancy on the course of the disease, the effect of the disease on the management of the pregnancy, and the possible hazards to the fetus of both the disease and its treatment, are all discussed. Among the 12 disorders are included diabetes, heart disease, renal disease, endocrine disorders, and there is a particularly useful review of lupus erythematosus and related conditions.

In general the authors adopt a positive attitude to pregnancy. However, the chapter on heart disease is directive and dogmatic, with pregnancy being firmly contraindicated in Marfan syndrome without qualification. There is no mention that many physicians are prepared to encourage mildly affected women to continue a pregnancy.

The authors are all from the USA, but the book crosses the Atlantic satisfactorily. It should find a place in obstetric departmental libraries, and is one to have to hand in the antenatal or family planning clinic. General practitioners with an interest in obstetrics would also find it useful.

A. Caroline Berry

Illustrated Textbook of Obstetrics edited by Geoffrey Chamberlain, Charlotte Gibbings & John Dewhurst. Gower Medical Publishing Company, London, 1988, 263 pages with figures and tables, £13.50

Titles for undergraduate textbooks have limited scope and all seem to have a familiar ring, but this is an illustrated textbook that certainly lives up to its name. There are a multitude of line drawings, graphs, flow charts, lists and diagrams, produced in three attractive toning shades, all pleasing to the eye and mostly enhancing the text. Perhaps the first chapter best exemplifies the way the illustrations complement the text: embryology is set out in a simple but comprehensive and lucid way. It is often a perplexing subject for the student, as is fetal physiology, but the illustrations are of particular help in these sections.

The authors obviously wished to produce a book that the student could carry around with ease (although not in a white coat pocket) and it cannot therefore cover all subjects, but it is sad that yet another undergraduate text omits a section on the placenta. One suspects that maternal physiology was compressed into two pages (although anatomy warranted five) from considerations of overall length.

It is very difficult to find an appropriate name for the healthy physiologically pregnant woman since patient surely refers properly only to the woman whose pregnancy is complicated by pathology, and the authors, as others, have not found an alternative to 'patient' although 'pregnant woman' is used interchangeably from time to time. On the other hand 'partner' has here replaced 'husband' in keeping with social change.

This text will undoubtedly appeal to students, with its clear didactic approach, but those who want to explore further and seek explanation and justification of certain points would find a 'suggested reading' list of use, or even references to two or three good review articles. The inclusion of a chapter relating to the fetus at risk is most helpful, drawing together as it does various threads, although alcohol has not been included. In the list of investigations carried out at the booking clinic it is implied that all women are tested for HIV without any comment regarding counselling or consent; this list also includes a 'Wasserman'—now replaced by VDRL in many units.

The care of the newborn is most thoroughly and appropriately included, but one wonders whether the detailed instructions about various operative procedures are pertinent in an undergraduate text. Obstetrics is exciting not least because of new developments, some of which become obsolete more quickly than textbooks can be produced, and maybe fetoscopy and biochemical assessment of fetal well-being come into this category. Do the authors not measure fundal height? And would a glossary help? But these are minor quibbles. This book will undoubtedly become popular with undergraduates and hopefully enthuse some to consider a career in this most exciting specialty. The fact that my review copy disappeared so rapidly from my office testifies to its immediate appeal.

Gillian Turner

Books received some of which may be reviewed at a later date

Legal Issues in Human Reproduction edited by Sheila A. M. McLean. Gower Publishing Company, Aldershot, 1989, 238 pages, £25.00

Fetal and Neonatal Development (Research in Perinatal Medicine VII edited by Colin T. Jones. Perinatology Press, Ithaca, New York, 1988, 675 pages with figures and tables, US $96.00 (list price $120.00)

Frontiers in Reproductive Endocrinology and Fertility edited by Charles S. A. Ng, F. H. Maurine Tsakok, S. L. Tan & K. H. Chan. Kluwer Academic Publishers, Dordrecht, 1988, 112 pages with figures and tables, Dfl 94.00, US $44.00, UK £25.00

Advances in Reproductive and Perinatal Medicine edited by W. C. Cheng & S. L. Tan. P. G. Publishing, Singapore, 1988, 171 pages with figures and tables, no price given

Depression after Childbirth by Katharina Dalton. Oxford University Press, 1989, 166 pages, £4.95

Baillière's Clinical Immunology and Allergy. International Practice and Research Vol. 2, Number 3, Immunological Disease in Pregnancy (October 1988) edited by P. M. Johnson. Baillière Tindall, London, Philadelphia, 527–795 pages, £17.50

Osteoporosis: Prevention, Management and Treatment by Harris H. McIlwain, Debra Fulghum Bruce, Joel C. Silverfield & Michael C. Burnette. John Wiley & Sons, Inc., New York, Chichester, 1988, 150 pages, £6.40

Proceedings and Symposia

AIDS and Obstetrics and Gynaecology (Proceedings of the nineteenth study group of the Royal College of Obstetricians and Gynaecologists, March 1988) edited by C. N. Hudson & F. Sharp. Published for the RCOG by Springer-Verlag, London, 1988, 352 pages with figures and tables, £57.80

Fertility and the Family The Glover Report on Reproductive Technologies to the European Commission by Jonathan Glover *et al.* Published by Fourth Estate, London, 1989, 166 pages, £7.95